MAR 15 1926 Medical Lib.

VOL. CLXXI, No. 3 MARCH, 1926 No. 648

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D., EDITOR
RICHARD A. KERN, M.D., ASSISTANT EDITOR

ESTABLISHED 1820

THE MORTALITY AND END RESULTS OF SPLENECTOMY. By WILLIAM J. MAYO, M.D. 313

CONCERNING THE CONFUSION BETWEEN ACUTE LEUKEMIA AND INFECTIOUS MONONUCLEOSIS. WITH THE REPORT OF A CASE OF ACUTE LYMPHOBLASTIC LEUKEMIA WITH REMISSION. By H. P. SCHENCK, M.D., and O. H. PERRY PEPPER, M.D. 320

THE INFLUENCE OF REST, SLEEP AND WORK UPON THE ACTION OF THE HEART. By LEO KANNER, M.D. 331

THE POSITIVE CENTRIFUGAL VENOUS PULSE. WITH A NEW METHOD FOR ITS DETECTION. By WILLIAM S. MIDDLETON 341

RAYNAUD'S DISEASE. LIMITATIONS OF THE CLASSICAL PICTURE AS A GUIDE TO DIAGNOSIS; REPORT OF A CASE SHOWING EXTENSIVE BONE INVOLVEMENT. By JAMES JOHN MONAHAN, M.D., F.A.C.S. 346

THE RESPONSE OF THE NORMAL HUMAN STOMACH TO VARIOUS STANDARD FOODS AND A SUMMARY. By PHILIP B. HAWK, M.D., MARTIN E. REHFUSS, M.D., and OLAF BERGEIM, M.D. 359

SOME REASONS FOR POOR RESULTS FOLLOWING GASTRO-INTESTINAL SURGERY. By RUSSELL S. BOLES, M.D. 369

THE PROPER CLASSIFICATION OF THE CEREBRAL PALSIES OF EARLY LIFE. By B. SACHS, M.D. 376

INCIPIENT GENERAL PARALYSIS. A STUDY OF THE EARLIEST SYMPTOMS PRESENTED BY SEVENTY-FOUR CASES. By HENRY A. BUNKER, JR., M.D. 386

ALCOHOLIC INJECTIONS INTO NERVE TISSUES FOR THE RELIEF OF PAIN. By GEORGE I. SWETLOW, M.D. 397

FUNCTION OF THE AUTOGENOUS KIDNEY TRANSPLANT. By KENJI IBUKA, M.D. . 407

FUNCTION OF THE HOMOGENOUS KIDNEY TRANSPLANT. By KENJI IBUKA, M.D. . 420

RENAL SEPSIS ASSOCIATED WITH MANIC DEPRESSIVE INSANITY. By EDWARD F. KILBANE, M.D. 433

INDEX TO ADVERTISERS . . . . . ADV. PAGE 42

Contents continued on page x

OWNERS AND PUBLISHERS
Philadelphia LEA & FEBIGER New York

COPYRIGHT, 1926, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER

PUBLISHED MONTHLY. SUBSCRIPTION, SIX DOLLARS A YEAR, POSTPAID

INFANT DIET MEAD'S MATERIALS

CO-OPERATION

In Infant Feeding

SUCCESS in Artificial Infant Feeding depends largely upon the kind of food selected, and *co-operation* with the mother.

There are many things that the doctor would like to tell the mother, and so we have devised a little book that gives the information just as the doctor would like to tell it himself. The title of this book is

"Instructions for Expectant Mothers and the Care of Infants"

The Subjects Covered Are:

Before Baby Comes
Urinary Examinations
Physical Examinations
Clothing for Expectant Mothers
The Bowels
Sleep
The Bath
Exercise
Diet
Care of the Teeth
When Baby Comes
Baby's Clothes
After Confinement
Nursing Your Baby at the Breast
Hours to Feed
Utensils Needed for Bottle-Feeding
Care of Cow's Milk
Care of the Nipples and Bottles
Orange Juice
Cod Liver Oil
Weighing the Baby
Baby's Bath
Sleep
Sunlight
Thumb and Finger Sucking
Pacifiers
Bed Wetting
Adenoids
Earache
Colds

Throughout the booklet no instructions are given, and the mother is urged to

CONSULT THE DOCTOR FIRST

There is no advertising of Mead's Products

25 to 50 copies of this little booklet will be sent to any physician on request.

MEAD JOHNSON & COMPANY, Evansville, Indiana, U. S. A.
Manufacturers of Infant Diet Materials

THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

MARCH, 1926

ORIGINAL ARTICLES.

THE MORTALITY AND END RESULTS OF SPLENECTOMY.

By William J. Mayo, M.D.,

ROCHESTER, MINN.

Before recommending the removal of a diseased spleen the physician must satisfy himself (1) that cure by medical measures cannot be expected, and (2) that the prospects of cure by splenectomy are sufficiently good to make the operation worth the immediate risk to the patient.

My purpose in this communication is to analyze briefly, from the standpoint of operative mortality, the experience with 417 cases in which splenectomy was performed, and to comment on the after history of the patients as related to the value of the operation.

The spleen is a hemolymph gland which belongs to the reticuloendothelial system, and has three known functions. The first is to filter from the blood stream microörganisms and various toxic agents, which it destroys or sends to the liver for destruction or detoxication. The spleen's failure to function as a filter results in its enlargement, of which that due to malaria and syphilis and the chronic toxic splenomegaly of the splenic anemia type are characteristic. The second function is to produce white blood cells, one of the most important being the lymphocyte, without which there would be no healing of wounds or repair in the body. All of the white blood cells have defensive functions, especially the large mononuclear endothelial leukocyte. In cases of leukemia a malignant expression is manifested in the unlimited production

of white blood cells which have the power of oxidation through their nuclear activities, but are without function owing to the lack of cytoplastic control. The third function is to destroy worn-out or deteriorated red blood cells, in the process of which bile pigments are found. An unnecessary destruction of the red blood cells which produces the suboxidation of anemia is one result of excessive splenic activity due to an increase in the size of the spleen from whatever cause. A specific action of the spleen on red blood cells is seen in its destruction of red cells with increased fragility, as in cases of hemolytic icterus, and in the destruction of the blood platelets, which is characteristic of chronic hemorrhagic purpura. Possibly the large spleens in these two conditions, as well as in certain other conditions, are to some extent the result of "work hypertrophy."

Sufficient clinical experience is now at hand to demonstrate beyond peradventure that in a number of diseases which otherwise would prove fatal, removal of the spleen has justified itself by curing them.

The statistics of early splenectomy show that the mortality was formerly from 25 to 35 per cent. The number of cases not being large, it is fair to assume that the high death rate led to delay in operation, until the patient's condition grew so serious that splenectomy was more than justified as a last resort. A vicious circle was thus established in which the high mortality brought about a delay responsible for a still higher mortality. Operative methods in the early history of splenectomy left much to be desired, but better technique, of which Balfour's method[1] of splenectomy is a fine example, has greatly reduced the surgical death rate.

From April 1, 1904, to January 1, 1926, splenectomy was performed in this Clinic in 417 consecutive cases, with an average hospital mortality of slightly more than 10 per cent. All the deaths that occurred in the hospital, without regard to the cause or the time, are included. If one adopted the thirty-day rule, that is, considered that if death took place more than thirty days after operation without surgical complication it was not an operative death, there would be a marked improvement in these statistics; but, unless an arbitrary method of classifying mortality is adopted, the tendency is, unconsciously perhaps, to "improve" the statistics. Moynihan, speaking of comparative statistics, says: "Statistics can be made to tell anything, even the truth." Certainly the method of computing hospital mortality with operative mortality at least gives the worse side of the picture. In the following tabulation the cases are classified on a clinical rather than a pathologic basis.

[1] Balfour, D. C.: The Technique of Splenectomy, Surg., Gynec. and Obst., 1916, **23**, 1.

SPLENECTOMY (APRIL 1, 1904, TO JANUARY 1, 1926).

Cause.	Cases.	Hospital mortality, cases.	Per cent.
Disease of the spleen due to infection and toxic agents	190	29	15.3
Abnormality of the white blood cells	50	2	4.0
Abnormality of the red blood cells	147	7	4.8
Splenic neoplasm	10	3	30.0
Surgical accident	10		
Indefinite and unclassified	10	1	10.0
Total	417	42	10.3

In the series of 417 cases splenectomy was performed in 190 for conditions the result of infections or toxic agents. The average mortality for this group was 10 + per cent. Studying these cases more in detail, it was found that there were 10 in which a greatly enlarged spleen was removed for chronic syphilis accompanied by profound anemia. Prolonged treatment had failed to obtain and maintain a cure of the syphilis. There was 1 death in this series. Spirochetes and syphilomas were found in most of the spleens, and often gumma in the liver also. These patients were promptly relieved of all signs and symptoms of syphilis as well as of the anemia, and have maintained good health.

Splenectomy was performed in 8 cases for tuberculosis of the spleen, with 1 death. Although it is altogether possible from what we know of tuberculosis that these 8 patients had tuberculous foci elsewhere, careful physical examination disclosed none, and the patients have all remained well. The one death was probably the result of surgical accident. While the spleen was being removed a tuberculous abscess of considerable size was ruptured with more or less soiling of the field. Instead of tying the vessels of the splenic pedicle separately, which would have been wise, I tied with a ligature on a needle, piercing a vein and probably carrying tuberculous material directly into a venous channel, since the patient died with generalized miliary tuberculosis.

There were 24 cases of septic splenomegaly in which splenectomy was performed, with 7 deaths. Again 1 patient died from general sepsis. In this case also a difficult pedicle was tied in a septic field by a ligature-carrying needle. The patients in this group all had active infection primary in other parts of the body, such as osteomyelitis and septic endocarditis, with the spleen greatly enlarged secondarily. It was hoped that by removing this extensive source of secondary infection the patient might be given an increased chance of overcoming the primary focus, and this occurred in some of the cases. However, all the patients with septic endocarditis died, either in the hospital or within a few months after dismissal.

Looked on as a whole, the picture of septic splenomegaly is discouraging. The hospital mortality of splenectomy is high and the

percentage of cures low. While this does not argue that splenectomy should be abandoned in this condition, it does imply that patients should be chosen for the operation with care, and that if possible, operation should be postponed until sufficient immunity is established to render it relatively safe.

While many enlarged spleens were removed from patients who had had malaria previously, in none could the plasmodium be discovered in the blood or in the splenic tissue, and these cases have therefore been classified under splenic anemia.

For splenic anemia splenectomy was performed in 114 cases, with 13 deaths. Analysis of the syndrome of splenic anemia suggests that the enlargement of the spleen primarily is due to infective or toxic agents, and one may assume that if the causative agent is a microörganism, it had been destroyed through natural agencies, since in these cases bacteria could not be cultured from the spleens removed. Yet the condition of the spleen with its thrombophlebitis, atrophy of the pulp cells, and widespread infiltration with connective tissue, was remarkably like that found in the spleens removed in the septic and the syphilitic groups. In each case explored the spleen was removed regardless of consequences. Some of the very large spleens were so adherent, especially up under the diaphragm, that enucleation rather than removal was necessary. Possibly the operation should have been abandoned under such circumstances, but who can tell? At least there were more triumphs than defeats, even in the terminal conditions.

In 2 of the earlier cases of splenic anemia the patients died from hemorrhage or shock as a result of hemorrhage, within forty-eight hours after splenectomy. We had not then sufficiently learned the two most important lessons in surgery: *See what you are doing*, and *leave a dry field*. With our present knowledge the mortality in this group should not exceed 5 per cent.

The fact that the liver is so often involved in secondary portal cirrhosis in the terminal Banti stage in these cases suggests that toxic agents collected or manufactured in the spleen and sent to the liver might be the cause of the diffuse deposit of connective tissue in the liver—as though the liver in its endeavor to encapsulate poisons which it was unable to detoxicate or eliminate, brought about the cirrhotic condition. Many patients of this group had ascites and edema of the lower extremities, and were generally in such condition that any operative procedure carried great risk. Because we have had a number of cures under these most discouraging circumstances the operation is justified, even at the expense of unpleasant operative statistics. When one sees patients with profound anemia, hemorrhages from the stomach, portal cirrhosis and ascites recover after operation and remain well many years, it takes more courage to refuse to operate than to operate.

The majority of the deaths which occurred in the hospital imme-

diately after operation were caused by progressive thrombosis from the splenic pedicle reaching the portal system or the superior mesenteric veins. Ten per cent of the patients dismissed from the hospital died within the next ten years from secondary hemorrhages, usually from the stomach.

The spleen was removed in 19 cases of primary portal cirrhosis, with 6 deaths, a high mortality. Perhaps as good ultimate results could have been procured more safely by procedures based on the Talma-Morison operation, with which we have had some satisfactory experience.

We were led to remove the spleen in cases of primary portal cirrhosis and secondary enlargement of the spleen by reason of the good results that followed splenectomy in the Banti stage of splenic anemia. It was thought that removal of the spleen not only would prevent toxic material from reaching the liver, but also would reduce the amount of blood in the portal circulation, thus relieving the load on the liver, and that the bed from which the spleen was removed would afford large areas for the development of collateral circulation.

In the clear-cut case of splenic anemia the enlargement of the spleen is noted long before symptoms of liver involvement develop, if at all. With primary portal cirrhosis, which evidently has its origin in toxic material from the gastrointestinal tract, enlargement of the spleen occurs late, and, as a rule, is much less marked than with splenic anemia. There are some cases, however, in which it is difficult to determine whether the gastrointestinal tract or the spleen is the primary source of the infection, and in a careful consideration of all the facts, splenectomy should be included. Certainly a number of these patients were greatly improved following splenectomy, have remained in good condition and are able to work. The high mortality and poor end results in this group of primary portal cirrhosis, as contrasted with those in the group of secondary portal cirrhosis of splenic anemia, are to be regretted, but when one considers the hopeless condition of the patients, and that several of the 6 deaths which occurred were delayed and had no direct connection with the operation, one derives some consolation if not satisfaction.

Splenectomy was performed in 15 cases of biliary cirrhosis, with 1 death. The type of biliary cirrhosis concerned is a curious condition in which chronic obstructive jaundice appears with a greatly enlarged liver and enlarged spleen, but without evidence of that infection of the gall bladder or common duct which accompanies the ordinary type of biliary cirrhosis so familiar in gall-stone disease. The gall bladder was not greatly distended, and did not show gross evidence of disease in any of these cases. The common duct was thickened in all cases, although in the cases in which it was opened and examined its caliber, as a rule, was not greatly

increased; thickening of all the bile ducts seems characteristic of the disease.

Some of these cases might be called Hanot's cirrhosis, if one could judge from Hanot's description just what was meant, and it is possible that some of the cases were atypical hemolytic icterus or were confused with it. Surveying the group as a whole, it is to be noted that the jaundice, unlike hemolytic icterus, was obstructive, that is, there was bile in the urine and the stools were clay colored. There were no gall stones, which are present secondarily in hemolytic icterus in 68 per cent of cases, without regard to the age of the patient. Again, in no case did the jaundice clear up completely, although it became less marked and occasionally indistinct, but the anemia disappeared, and most of the patients were able to return to their work.

The spleen was removed in 50 cases in which the splenomegaly clinically was concerned chiefly with the white cells, with 2 deaths. In cases of leukemia there is a pathologic increase in the production of white cells by all the reticulo-endothelial tissues. In splenomyelogenous leukemia the spleen is perhaps the chief source of the white cells, but not the only one. Forty of the 50 cases in which splenectomy was performed were of splenomyelogenous leukemia, with regard to which some interesting facts were developed. If the spleen is reduced by Roentgen ray and radium in such cases it can be removed without much risk. In all the cases immediately following removal of the spleen, which was greatly enlarged and burdensome, the white cells promptly decreased from an average of several hundred thousand to less than 100,000 and often to less than 50,000. Some of the patients have been able to continue their work and support their families for more than five years, although the blood has not become normal.[1] In most cases, however, after temporary improvement the disease pursued its fatal course.

In removing the spleen in cases that at first had been favorably affected by radium and Roentgen ray, but not later, it was noticed that the spleen had become greatly changed in its outer layers; changes which acted, so to speak, as a protective capsule around the active splenic substance, and the failure to secure better results from radiotherapy is probably due to this action.

In young persons in the early stages of splenomyelogenous leukemia, and especially in the atypical types, splenectomy is well worth consideration. Reduction of the size of the spleen by radium and Roentgen ray previous to operation is advisable.

In 4 cases the spleen was removed for lymphosarcoma, with rather surprising results. There were no deaths, although the spleens were huge, and the patients lived for considerable lengths

[1] This is much the most favorable report on splenectomy in leukemia with which we are acquainted.—Ed.

of time. One patient, a young married woman with one child, lived nearly eight years, raised two children, and died from lymphosarcoma which had metastasized to the lungs.

In 1 case of enlarged spleen, which proved to be Hodgkin's disease, splenectomy was performed without particular benefit, and the patient died within the year.

There were 3 cases of lymphoma in which the very large spleen was removed with permanently good results.

For conditions caused by abnormalities of the red blood cells the spleen was removed in 147 cases, with 7 deaths. In such cases splenectomy is most effective.

Splenectomy was performed in 69 cases of hemolytic icterus, all showing more or less fragility of the red cells, which persisted after splenectomy, with 4 deaths. Two of the deaths it is difficult to ascribe to the operation. The 65 patients were cured and have remained well. Gall stones were present in 68 per cent, even in young patients.

The spleen was removed in 11 cases of hemorrhagic purpura, with no deaths. Before operation there was a reduction of blood platelets from a normal of between 225,000 and 400,000 to between 80,000 and 10,000, and while the platelets after splenectomy usually came up to normal or above, in some cases they remained below normal. These patients were all immediately relieved by the operation and have remained well.

The spleen was removed in 1 case of polycythemia apparently in the terminal stages. Although the spleen was unusually large, there was a remarkable restoration to health which has lasted for more than four and a half years.

There were 62 cases of pernicious anemia in which splenectomy was performed, with 4 deaths. The deaths occurred in the earlier cases in which operation did not appear to be justified until the condition of the patient was precarious. In the last 40 cases there were no deaths. The greater number of these patients were operated on soon after Eppinger made his classical report, and a period of four years elapsed in which we did not perform splenectomy for pernicious anemia. However, when Giffin studied the postoperative histories of these patients he found that comparable patients for whom splenectomy had been performed had lived two and a half times as long as those who had not been operated on, and some were alive and in fair health more than five years after operation. It is probable that some of the earlier cases classified as pernicious anemia were in fact cases of aplastic anemia, for which splenectomy is of no avail.

Among young patients otherwise in good condition and in the earlier stages of the disease, splenectomy is worth a trial in selected cases and especially in the atypical cases. One gets the idea that the spleen is not primarily concerned with pernicious anemia, but

that in the course of the day's work it destroys deteriorated red blood cells, which in pernicious anemia though deteriorated are still capable of maintaining life and are the best the bone marrow can produce. In no case did the blood return to normal after splenectomy.

Ten cases of splenomegalia were not classified from lack of sufficient knowledge as to the cause of the enlarged spleen, and it is probable that with increasing knowledge we shall find that a number of other cases have been incorrectly classified. In 20 cases the spleen was removed for splenic neoplasm and traumatism.

Summary. A survey of the foregoing experience demonstrates clearly that removal of the spleen is compensated for by the widespread tissues of the reticulo-endothelial system, of which physiologically it is a none too important part. The diseases with which the spleen is concerned are complex and pathologic processes are seldom primary in the spleen; it often acts merely as an agent of destruction.

From the surgical standpoint, it can be said that if a patient is properly rehabilitated and on the up-grade, the result of proper methods of preparation, the mortality of splenectomy will be less than 5 per cent. No patient should have the spleen removed for chronic conditions when he is on the down-grade, as we found out by bitter experience. The dangers of the operation are largely in delay and in an unfortunate choice of cases.

CONCERNING THE CONFUSION BETWEEN ACUTE LEUKEMIA AND INFECTIOUS MONONUCLEOSIS.

With the Report of a Case of Acute Lymphoblastic Leukemia with Remission.

By H. P. Schenck, M.D.,

and

O. H. Perry Pepper, M.D.,

(From the Medical Clinic of the Hospital of the University of Pennsylvania.)

Considerable attention has in the past five years been centered upon the similarity of acute leukemia and infectious mononucleosis one to the other and upon the differential diagnosis between them. Confusion still exists and threatens to become worse with the introduction into the literature of another somewhat similar syndrome under the name Agranulocytic Angina. The records of carefully studied cases of these conditions are needed and for this reason this review and case report are being presented.

The confusion which exists in this field finds its origin, as is so often the case, in bewildering terminology, mistaken translations and in the reports of incompletely studied cases. Several fundamental difficulties enter into the matter; the most important of which concern the classification and identity of the very different types of white blood cells which by various writers have been at times grouped under the loose heading "mononuclear."

A very brief survey of the literature makes it clear at once that under this term have been included the following: Lymphocytes, lymphoblasts (large lymphocytes, and so forth), myeloblasts, monocytes (large mononuclears, transitional cells, endothelial leukocytes, and so forth). No wonder confusion exists, especially when a writer in one language employs a term with one meaning and the translator in another. The second important source of confusion rests on the failure of many writers to distinguish between an actual and a relative increase of a given cell type in the blood. Many statements also are quoted incorrectly.

Let us start then by reviewing the terms to be employed and the conditions to be discussed.

I. The Cell Types Concerned. (*a*) The *myeloblast* is the only member of the granular or myelogenic series of white blood cells which could ever be included under the term "mononuclear" and is the most immature member of this series. For our present purposes this cell form may be said only to occur in the peripheral blood in leukemia; in small numbers in chronic myelocytic leukemia but in very large numbers in acute myelocytic or myeloblastic leukemia. In this latter instance the myeloblast must be distinguished from the corresponding lymphoblasts of acute lymphatic leukemia by the presence in the myeloblast of oxydase granules and of proteolytic ferment.

(*b*) The *lymphoblast* so closely resembles the myeloblast that special methods are required to distinguish them. It is the most immature form of the lymphatic series ever to enter the circulation and occurs in the largest numbers in acute lymphatic or lymphoblastic leukemia. All gradations between this cell and the mature lymphocyte of normal blood may be seen and in any condition of active lymphocytosis there is a tendency for younger, larger lymphocytes to appear in the blood.

(*c*) *Lymphocytes.* The mature lymphocyte is the small deeply staining lymphocyte of normal blood. Its younger forms are somewhat larger and have relatively more cytoplasm. In many reports these cells have been included under the term mononuclear only to have the figures quoted later in an article in which the term mononuclear was limited to the cells of the group next to be considered.

(*d*) *Monocytes.* These cells by some have been called endothelial leukocytes because of their endothelial origin, by others large

mononuclear cells and transitionals because they were once thought to give rise to the granular leukocytes (polymorphonuclear leukocytes). The term mononuclear has often been limited to that form of monocyte with the round nucleus and has also been used to include the form with the indented or kidney-shaped nucleus formerly called "transitional."

It is obvious that confusion will arise so long as the term mononuclear may be applied to any one or all of these forms. Mononuclear is not synonymous with monocyte nor can it be safely used at all unless defined in each case. It had best be dropped altogether from hematological literature. There is no need for the limited terms mononuclear and transitional; these can both be included under monocyte, nor is there any valid excuse for using the term mononuclear to cover the whole group of cells which happen to have a single unbroken nucleus.

Before proceeding a word should be said about simple lymphocytosis. Confusion has arisen through a failure to distinguish between a relative and an absolute lymphocytosis and through the inclusion of lymphocytes under the term "mononuclears." Relative lymphocytosis occurs with great frequency as a result of a neutrophile leukopenia and the emphasis should be placed on the primary reduction in the neutrophile count and not on the wholly secondary relative increase in lymphocyte percentage. The list of conditions usually given in which lymphocytosis occurs is largely a list of conditions in which neutrophile leukopenia is present. A disappearance of neutrophile and other granular leukocytes leaves behind only the lymphocytes and monocytes and this state of the blood has unfortunately often been referred to as a mononucleosis.

An actual lymphocytosis of any considerable degree occurs in but few conditions. In pertussis a total white count up to 85,000 may occur with even 95 per cent of mature lymphocytes, a picture which might well suggest chronic lymphatic leukemia. Crombie[1] has reported 2 cases of whooping cough in infants with much higher counts; one with 113,000 with 67 per cent of lymphocytes, the other with 233,000 total white cell count of which 58 per cent were lymphocytes.

II. *Conditions in which confusion arises as a result of changes in the white blood-cell picture involving the cell types just enumerated.* These include the following:

(*a*) *Acute Leukemia.* The predominant cells of the myeloblastic and lymphoblastic types of acute leukemia when stained with eosin-methylene azure stains can usually not be told apart and more study is required to identify the type of leukemia. There should be little or no confusion, however, between the blood picture of simple lymphocytosis or chronic lymphatic leukemia with that of acute leukemia in which the larger immature lymphocytes and lymphoblasts with more cytoplasm and less deeply-staining nucleus form

the greater part of a total count which as a rule rises well above 50,000 and often exceeds 100,000 per cm.*

(*b*) *Infectious Mononucleosis.*[2, 3] In this disease which may be identical with what was formerly called glandular fever, and which is usually or always associated with a Vincent's angina, there occur marked changes in the blood picture. Many of the cases, though not all, have a leukocytosis which occasionally exceeds 20,000, and is due to an increase of the cells of the lymphocyte series both mature, immature and perhaps abnormal. Often 70 or 80 per cent of the total number of white cells are apparently normal mature lymphocytes. At other times there are a greater number of larger cells which suggest immature lymphocytes or even lymphoblasts. It is these cells which lead to the suspicion of acute leukemia.[4]

The term mononucleosis as applied to this disease is unfortunate. Those who limit the term mononuclear to a type of monocyte will be misled into expecting an increase of these cells. Some term expressing the lymphocytosis would be preferable, several have been suggested, for example, acute benign; lymphoblastosis,[5] acute lymphadenosis.[4]

On the one hand the blood picture of infectious mononucleosis may be confused with that of acute leukemia and on the other hand with simple lymphocytosis. This will be discussed later.

(*c*) *Agranulocytic Angina.* A recently coined term to describe a condition of angina with leukopenia due to the disappearance from the circulating blood of all or almost all of the white cells belonging to the granular or myelogenic series, in other words, a neutrophile leukopenia with, of course, a relative lymphocytosis or as some would say "mononucleosis." The reported cases have most of them had counts well below normal, some as low as 900 per cm. with as high as 98 per cent lymphocytes; but in a few cases[6] reported under this heading the total count has been normal or even above normal for at least part of the illness. For example, one of Zadek's cases had a total count of 17,100, of which 86 per cent were lymphocytes. This case which perhaps was one of infectious mononucleosis recovered promptly, whereas the cases reported with characteristic leukopenia all die. One case reported by Moore and Wieder[7] recovered from her first attack in which the count fell to 1200, but succumbed to a second attack two years later.

Most of the case reports of agranulocytic angina have been from Germany,[8, 9, 10, 11, 12, 13] but a few cases have been reported elsewhere.[14, 15, 16, 17, 18]

It is immediately apparent that these cases resemble closely the picture presented by any overwhelming infection in which there occurs a neutrophile leukopenia. On the other hand, the few cases without leukopenia come closer to infectious mononucleosis and in Skiles' case Vincent's organisms were found in the angina.

* In the aleukemic or leukopenic stages greater difficulties are presented.

Discussion. The confusion in this field is of long standing and many aspects. For example, in 1907, Türk[19] saw a patient with tonsillitis and adenopathy, in whom the white cell count was 16,700 and the lymphocytes constituted 85 per cent of the number. Turk made the diagnosis of acute lymphatic leukemia and gave a bad prognosis. The patient recovered and in the light of our views today was probably a case of infectious mononucleosis

It was from such cases that the statement of a lymphocytosis in septic infection arose, as Tidy[20] has pointed out. Many of the cases of so-called sepsis were probably infectious mononucleosis, others perhaps leukemia. Not one according to Tidy supports the statement of an actual lymphocytosis in septic infection. Marchand's[21] Case VI and Cabot's[22] Case XII both strongly suggest the picture of infectious mononucleosis.

Of course, relative lymphocytosis does occur in severe septic infection as a result of the neutrophile leukopenia and this also has led to confusion just as the same picture has in aplastic anemia, benzol poisoning and the other conditions in which there is a lessened bone-marrow activity. Insofar as the blood picture is concerned there is no difference between that of neutrophile leukopenia on the one hand and that of so-called agranulocytic angina on the other. That agranulocytic angina is said to occur chiefly in middle aged or elderly women is surely not distinctive and an insufficient number of bacteriological examinations are on record to permit any statement on this phase. The fatal outcome is in keeping with what would be expected in any infection overwhelming enough to reduce the count of circulating white cells to this degree. That the infection in so-called agranulocytic angina is chiefly in the throat and mouth does not influence the argument, but does help to cause confusion with infectious mononucleosis, scurvy and acute leukemia, especially if the latter be in the stage with little or no increase of white blood cells.

It is true that acute leukemia may be present for a time without any great increase in the white blood-cell count and during this stage the differentiation from infectious mononucleosis may be very difficult. Some believe that the differential diagnosis can be made from a careful study of the predominating type of cell,[4] but this is very difficult. Acute leukemia may occur at any age in either sex; infectious mononucleosis has been recognized most often in young males, many of them medical students, but it is probably a matter of the care of study of such cases. There is nothing about the glandular enlargement to differentiate the two conditions except perhaps the greater tendency for the adenopathy to be limited in infectious mononucleosis to the cervical and submaxillary glands. The discovery of Vincent's organisms does not settle the matter, but does create a hope that the condition is "infectious mononucleosis." Perhaps the total white-cell count

will first settle the diagnosis. No case of unquestioned infectious mononucleosis has been reported in which the total white cell count approached that usually seen in acute leukemia. By far the majority of cases of infectious mononucleosis have a white cell count below 30,000 per cm., while by the time a case of acute leukemia has definite adenopathy and a sore mouth the count is usually in excess of 50,000. Of course, aleukemic periods occur in the course of some cases of leukemia.

Anemia is a constant symptom of acute leukemia but has been present in only a few of the reported cases of agranulocytic angina (Zadek's Cases III and IV with 43 per cent and 29 per cent hemoglobin respectively). Anemia is not a part of the picture of infectious mononucleosis, but is very marked in aplastic anemia. Anemia, therefore, is of some diagnostic assistance.

The cause of acute leukemia is not known and there is nothing absolutely diagnostic about the mouth and throat lesions which occur in this disease. In these lesions many mouth spirillæ may be found, and Vincent's organisms may also be present, but there is no evidence that any of these organisms are the true cause of the disease. Vincent's angina has been reported in so many of the cases of infectious mononucleosis as to suggest that this syndrome is merely a reaction to this infection. Whether the agranulocytic angina may prove also to be due to Vincent's angina it is impossible to say. No mention of these organisms is made in most of the case reports. B. pyocyaneus was found in the throat lesions of several cases and from the blood in one. Such results are too few to draw any conclusions from.

In this brief review then it is made clear there exists confusion in the matter of cell types, in the terminology employed and in the differential diagnosis of these several syndromes. The following case is reported because it illustrates and helps to clarify some of these difficulties.

Case Report. F. R., male, aged twenty-one years, an American, was admitted to the Hospital of the University of Pennsylvania on October 30, 1924, complaining of continuous nosebleed and fatigue.

History of Present Illness. Two months ago he began to feel tired all the time. Four weeks ago he had "tonsillitis" and an eruption on the face which was said to have been "barber's itch." He recovered from this acute condition but continued to grow weaker and more fatigued. Six days ago there developed sudden epistaxis repeated daily, and sometimes lasting several hours. Dr. Thomas H. Llewellyn, who referred the patient to the hospital, diagnosed the case as Vincent's angina. In spite of treatment the bleeding continued, weakness increased and the patient fainted on the day before admission.

Previous Medical History. Unimportant.

Family History. Negative. No bleeding tendency in any relative.

Social History. The patient was a druggist. He took no drugs and had not been exposed to benzol. He used tobacco and alcohol moderately.

Positive Findings of Physical Examination (Dr. Schenck). The patient was pale and asthenic, dizzy and nervous. Blood oozed from the nose and there were petechiæ in skin of neck, trunk and extremities. The tonsils were enormous and hyperemic. There were some petechiæ in mucosa of the mouth, but no membrane or ulcers. There was slight enlargement of the submaxillary, submental, cervical, epitrochlear and inguinal lymph nodes. Hemic murmurs were heard over the base of the heart. The spleen was enlarged down to the level of the umbilicus. The liver edge could not be felt, but the liver was enlarged to percussion. Dr. Schenck's tentative diagnosis at this stage of the study of the case was: Acute lymphatic leukemia. Acute tonsillitis (symptomatic of the leukemia).

Laboratory Examinations. Urine analysis was unimportant; the phthalein test 55 per cent. Smears from the tonsils were negative for Vincent's organisms. Cultures showed streptococci of both hemolytic and non-hemolytic strains. The Wassermann test was negative.

Blood Examination. October 30, 1924. Hemoglobin 40 per cent; red blood cells, 2,100,000 per cm.; white blood cells 577,000 per cm. Differential count; Neutrophilic leukocytes, 0.7 per cent; eosinophilic leukocytes, 0.0 per cent; basophilic leukocytes, 0.3 per cent; myelocytes, 0.3 per cent; lymphocytes, 98.7 per cent and monocytes, 0.0 per cent. An oxydase stain confirmed this count; 98 per cent of the cells possessed no oxydase granules. Coagulation time of venous blood by Wright's method was 6.5 minutes. Clot retraction was abnormal, and failed to respond in six hours. Coagulation time of finger prick blood was one-half minute. Platelets numbered 239,000 per cu.mm. A tourniquet test was positive.

A study of the cells included in the above count under the heading lymphocytes showed them to range in size all the way from a small mature lymphocyte of normal blood to a much larger cell as big as the average myelocyte. In the larger cells the rim of cytoplasm was relatively greater and sometimes stained the light basophilic tint characteristic of the lymphocyte series, but in a few instances the cytoplasm had the deeper basophilic strain suggesting the irritation form of Türk. However, the entire group appeared to be lymphocytes and this is confirmed by the oxydase stain. It would seem quite proper to divide this group of lymphocytes into three headings: Mature lymphocytes, immature lymphocytes and lymphoblasts; but attempts to make such differential counts led to consider-

able confusion as the grading from one form to another was so gradual that it would require an arbitrary division. Myelocytes which were seen were mostly neutrophilic although an occasional eosinophilic myelocyte was found. The further course of the blood changes is shown in the charts on pages 328 and 329.

Diagnosis. These hematologic findings seemed to confirm the diagnosis of lymphatic leukemia. Such a high total count with such a degree of lymphocytosis is more common in chronic lymphatic leukemia than in the acute form, but the shortness of duration of the illness and a certain tendency of the lymphocytes to be larger and with relatively more cytoplasm than the usual mature lymphocyte argued strongly for the diagnosis of acute lymphatic or lymphoblastic leukemia.

Course of Disease. Although it was felt that the prognosis was almost hopeless, treatment was instituted as follows:

(*a*) Iron and arsenic hypodermically daily; (*b*) local treatment of throat with solution of silver nitrate; (*c*) blood transfusions; (*d*) neoarsphenamin intravenously.

At first there was but little improvement but soon very marked improvement occurred. The charts show the rapid drop in the leukocyte count and the correspondingly rapid improvement in the anemia. The number of transfusions and their amounts is noted in the charts.

Within two weeks after admission the patient's entire picture had changed. The bleeding had stopped, petechiæ and tourniquet test had disappeared, the patient's color had markedly improved and the spleen had lessened in size. The vision, which had been seriously impaired by retinal hemorrhages, had so far improved that the patient could now read. A very marked improvement in the retinal findings was noted by the consulting ophthalmologist, Dr. Thomas B. Holloway.

On November 15, there was a return of tonsillar ulceration and petechiæ, but this caused little or no setback in the steady progress of the case. There was, however, an increase in the size of the enlarged cervical and neighboring glands. The throat improved within three days. Examinations of material from the throat were all negative for Vincent's organisms.

A week later an earache developed and spontaneous rupture of the drum occurred with a small amount of discharge. It is interesting to note that on this date the red blood-cell count was over 4,000,000, the hemoglobin percentage 85, and the total white cell count 7100. Only the differential count revealed any abnormality, the high lymphocyte percentage persisting, 74 per cent of the total.

Another week of improvement passed. The spleen and lymph glands became smaller, the total white count dropped to 4800 and the ear condition subsided somewhat. At this time the change from the date of admission four to five weeks previously was amazing,

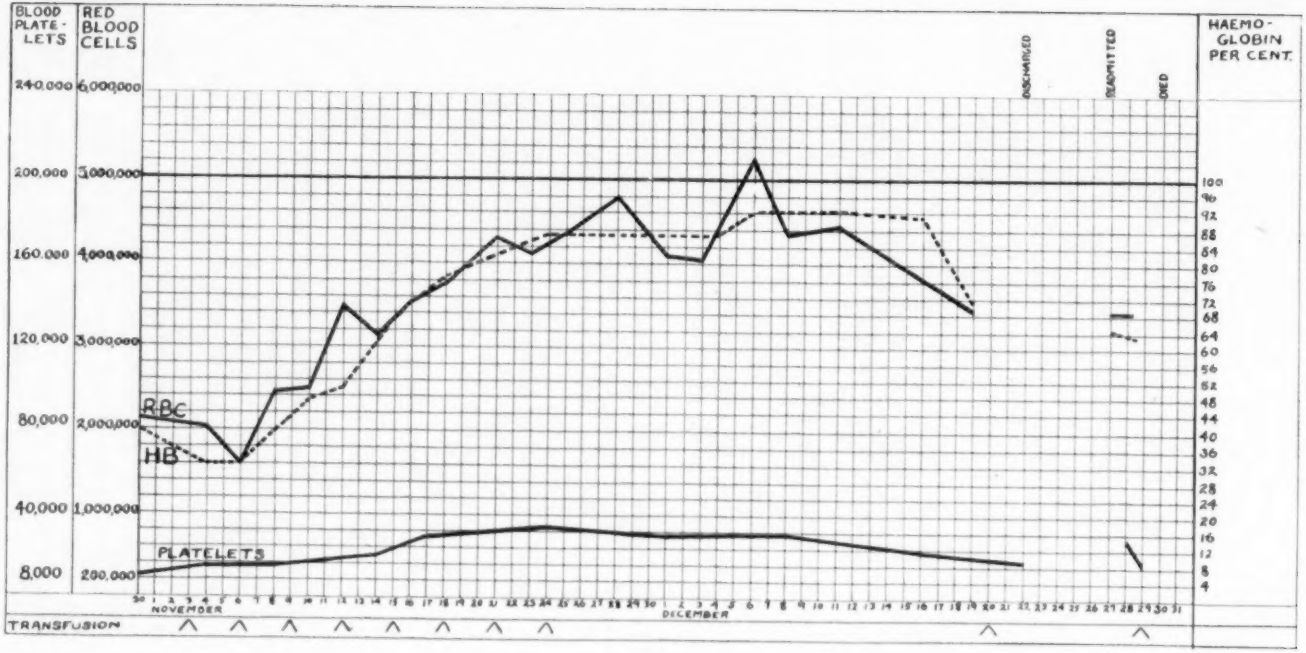
BLOOD PLATE-LETS
RED BLOOD CELLS
HAEMO-GLOBIN PER CENT.
DISCHARGED
READMITTED
DIED
240,000
200,000
160,000
120,000
80,000
40,000
8,000
6,000,000
5,000,000
4,000,000
3,000,000
2,000,000
1,000,000
250,000
100
96
92
88
84
80
76
72
68
64
60
56
52
48
44
40
36
32
28
24
20
16
12
8
4
RBC
HB
PLATELETS
NOVEMBER
DECEMBER
TRANSFUSION

CHART I

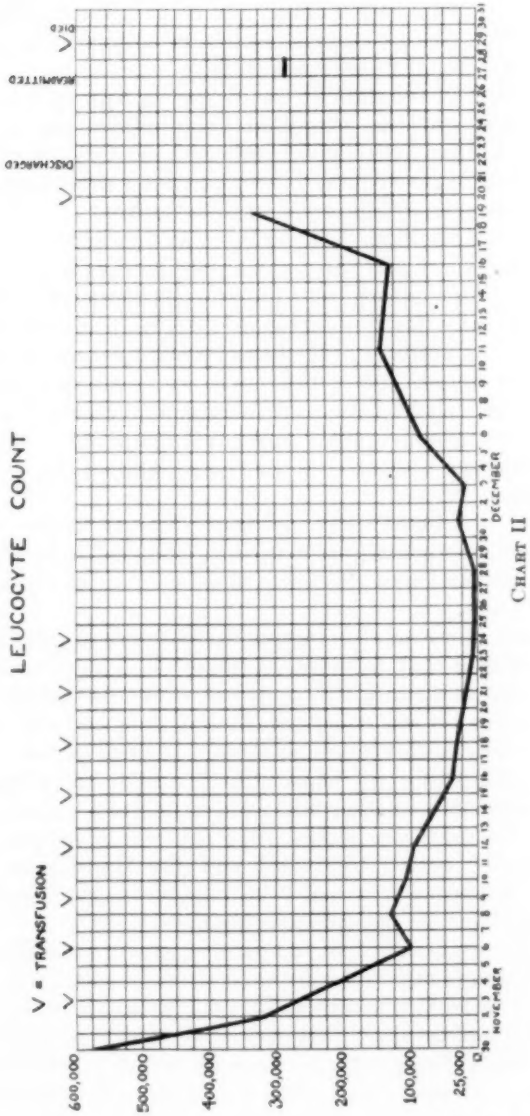

CHART II

and the diagnosis of leukemia had to be questioned, but the extremely high counts previously recorded seemed to force the maintenance of this diagnosis.

Active treatment was now lessened and transfusions stopped. No return of anemia was noted, but the total white count commenced little by little to rise. Within a week it rose from 4800 to 83,400 of which latter figure 79 per cent were lymphocytes. A week later

143,000 was reached; still without any drop in the red blood cells or hemoglobin. At this time petechiæ reappeared and the tourniquet test was found to be again positive.

On December 19 the patient was definitely less well; there were many petechiæ and the glandular enlargement was increasing. The white cells had risen to 333,400 and the red cell count and hemoglobin had begun to drop. New glandular enlargements made their appearance, especially a flat swelling in front of each ear suggesting a parotid swelling. The spleen was now very large. Hearing became less acute and the mental state approached coma.

A few days later oozing from the nose recommenced, and coma deepened. Finally death occurred in coma from cardiac failure.

Necropsy. At necropsy, the characteristic findings of lymphatic leukemia were found. All lymph nodes were enlarged and hemorrhagic; the spleen and liver were enormously enlarged and were infiltrated throughout with masses of lymphoid cells. There were hemorrhages scattered throughout various organs and on serous surfaces.

Discussion of Case. There are many reports in the literature of cases in which a diagnosis of acute leukemia had to be abandoned for one of infectious mononucleosis upon the cure of the condition (see Türk [19]).

In this case, however, the picture at first was so definitely that of acute leukemia that we were unwilling to change our diagnosis even when the total count fell to normal. The possibility of infectious mononucleosis was discussed at that time and this diagnosis ruled out because of the very high counts obtained at first. Remissions occur in almost every known blood disease, including chronic leukemia, pernicious anemia and even in acute leukemia, and in the present instance we believe that the remission was perhaps initiated by the active treatment and the transfusions. What would have happened if it had been possible to continue the free use of transfusions we can only speculate.

Even if the total count had not been so great, we believe that a study of the lymphocytes would have strongly suggested that the case was one of leukemia rather than one with simply an increase of normal lymphocytes. Certainly the blood picture differed from what might be seen in a case with simple lymphocytosis, as for example whooping cough; but did approach more nearly the blood picture of infectious mononucleosis. It is quite possible to believe that, certainly on the blood picture alone, it would be impossible to differentiate between certain cases of infectious mononucleosis and acute leukemia; and on the other hand, if the cases of whooping cough with very high total counts and lymphocytosis be accepted, it must be admitted that such a blood would be differentiated from a chronic lymphatic leukemia with great difficulty.

Summary. It is important in hematological reports to define just what is meant by the terms employed. Confusion has resulted from a failure to do this. Only by careful reports can the proper distinction between true lymphocytosis, acute lymphatic leukemia and infectious mononucleosis be made.

The syndrome agranulocytic angina does not apparently deserve to be considered a special entity but merely one type of reaction to severe infection.

A case of acute leukemia is reported, of the lymphatic or lymphoblastic type, in which during a remission, perhaps induced by treatment, the blood picture passed through stages at which it closely resembled infectious mononucleosis and even reached the stage where it resembled the picture of agranulocytic angina. A rapid return of the leukemic blood picture, however, followed with fatal outcome.

REFERENCES.

1. Crombie: Edinburgh Med. Jour., 1908, n. s., vol. **1**, p. 222.
2. Sprunt, T. P. and Evans, F. A.: Bull. Johns Hopkins Hosp., 1920, **31**, 357.
3. Longcope, W. T.: Am. Jour. Med. Sci., 1922, **164**, 781.
4. Downey, H. and McKinley, C. A.: Arch. Int. Med., 1923, **32**, 82.
5. Bloedorn, W. A. and Houghton, J. E.: Arch. Int. Med., 1921, **27**, 315.
6. Zadek, I.: Medizinische Klinik, 1925, **21**, 688.
7. Moore, J. A. and Wieder, H. S.: Jour. Am. Med. Assn., 1925, **85**, 512.
8. Bantz, R.: Medizinische Klinik, 1923, **19**, 23.
9. Lauter: Medizinische Klinik, 1924, **20**, 1324.
10. Elkeles: Medizinische Klinik, 1924, **20**, 1614.
11. Petri, E.: Deutsch. med. Wchnschr., 1924, **50**, 1017.
12. Leon, A.: Deutsch. Arch. f. klin. Med., 1923, **143**, 118.
13. Schultz, W.: Deutsch. med. Wchnschr., 1922, **48**, 1495.
14. Lovett, B. R.: Jour. Am. Med. Assn., 1924, **83**, 1498.
15. Hatzieganu and Goia: Bull. et mém. Soc. med. d. hôp. d. Paris, 1925, **49**, 69.
16. Skiles: Jour. Am. Med. Assn., 1925, **84**, 364.
17. Conrod, A. A.: Nebraska Med. Jour., 1925, **10**, 48.
18. Pelnar: Cas. lek. cesk., 1924, **83**, 1498.
19. Türk: Wien. klin. Wchnschr., 1907, **20**, 157.
20. Tidy: Quart. Jour. Med., 1924, **17**, 210.
21. Marchand: Deutsch. Arch. f. klin. Med., 1910, **100**, 552.
22. Cabot: Am. Jour. Med. Sci., 1913, **114**, 335.

THE INFLUENCE OF REST, SLEEP AND WORK UPON THE ACTION OF THE HEART.

By Leo Kanner, M.D.,

YANKTON STATE HOSPITAL, YANKTON, S. D.

(From the Second Medical Clinic of the Charité Hospital, Berlin, Germany.)

If, according to the procedure of Huerthle,[1] systole be determined as the time from the beginning of the first to the beginning of the second heart sound, then the proportionate duration of the

systole, the "time of action," compared with the time of the entire heart period, amounts to an average of 33.5 per cent to 37.5 per cent in the healthy adult with a pulse rate of between 50 and 78 beats in a minute, as Brugsch and Blumenfeldt[2] have found. From that, as calculated for the period of twenty-four hours, a working time of approximately eight hours results for the human heart, provided, of course, that within that term equal work, neither too hard nor too easy, be performed by the heart muscle. In order to ascertain whether and to what extent this "eight-hour working day" of the normal heart is altered by physically exhausting labor or, on the other hand, by rest in bed of longer duration and by sleep, and in order to find out what effect rest and motion exercise upon the time of action and upon the time of electric stimulation of the ventricles, electrocardiographic and cardiophonographic examinations were made of the same individuals, first in the usual condition, then in the state of rest and sleep, and finally immediately after the performance of increased muscular activity.

The investigations were made of individuals: (1) With healthy hearts; (2) with valvular diseases; (3) with tachycardia; (4) with bradycardia, persons of various ages and both sexes being selected.

All researches, having been preceded by case history, auscultation, percussion, Roentgen ray examination, and determination of the blood pressure, were done with Einthoven's string galvanometer and with Frank's cardiophonograph which was attached to the apparatus, so that each film contained two electrocardiographic (Derivations I and II), one cardiophonographic, and one chronometric curves.

Normal Curves. Of each person three films were made, the first in an "indifferent" condition of the heart, that is, just as the patient had come into the room, without having rested or done any hard work. In the following, we shall speak of these curves as "normal curves" or "usual day curves."

Sleeping Curves. The object of the second photograph was to observe the influence of prolonged rest and of sleep upon the action of the heart. To obtain this, the writer had the persons examined lie on their backs for one hour and a half in the darkened room, with avoidance of speech and all other movements, the electrode cuffs and the phonographic heart drum being left on. After that time the majority of the persons were found to be asleep. With the exception of 1 case where bromids were given, the writer abstained from the production of artificial sleep for fear of an eventual falsification of the result by the influence of the drug employed upon pulse rate and time of action. Not always, it is true, could the continuous psychic excitement, though diminished by suggestive means, be eliminated, especially in neurasthenic and psychopathic individuals, an excitement that was also partially based on the rather unusual situation. Therefore, only such persons were used

who either had gone through an electrocardiographic examination before or who prior to their own examination had watched that of another person so that they could convince themselves of the harmlessness of the procedure. In one of the cases a deviation from the rule was noticed when the noise of the starting motor awakened the patient, when, instead of the sleeping curve, one immediately after awakening was taken.

Resting Curves. In all those cases where sleep could not be obtained, it was tried at least to produce a sleep-like rest during which the subjects, according to their own statements, "dozed" or "drowsed." We shall speak of such photographs as "resting curves" and reserve the term "sleeping curves" for those cases where the examiner was fully convinced that the pictures were taken during regular sleep.

Working Curves. The second film was followed by the working experiment. The exertion consisted in most cases in about 20 to 25 deep genuflections, and where for some reason they appeared unsuitable, in pushing the arms forward, sideward, and upward, or in the movements of carpet beating, so that a noticeable fatigue with increase in the pulse rate resulted. In patients with advanced decompensation of the heart such procedures were naturally contraindicated. Here a repeated sitting up and lying down in bed was prescribed in order to obtain the effect desired. The pictures taken about thirty seconds after the termination of the movements will be called "working curves."

Influence upon the Time of Action. As the most important result of the valuation of the influence of rest, sleep and work upon the heart in the examination of 25 persons, there was an almost invariable correspondence of the time of action with the pulse rate. The absolute duration of systole is inversely—the proportionate duration of the systole, directly—proportional to the number of heart beats; the faster pulse corresponds with a longer time of action. As is well known, the pulse rate becomes lower in the condition of complete bodily rest with absence of psychic excitement—the writer has observed differences up to 36 beats in a minute—on the other hand, it is increased to more than one and a half times by physical exertion and coarse psychic emotions such as fear, fright, anger or expectation. Hence, with the slackened action of the resting heart, that is with the prolongation of the single heart period, an increase in the absolute, a decrease in the proportionate duration of the systole naturally corresponds, while during work the accelerated heart action results in a reversal of these conditions.

The time of action is reduced in the condition of rest, prolonged during work.

In the adult with a healthy heart the time of action amounts to 31 per cent to 35 per cent during rest and to 34.5 per cent to 39.5 per cent under the influence of work. Hence, deviations from the

normal average of 33.5 per cent to 37.5 per cent are present, but in the healthy adult not very considerable. The difference is for rest about − 2 per cent, for work up to + 7 per cent.

There exists, as is seen, a constant proportion between pulse rate and time of action, in that the influence of rest and work upon the proportionate duration of the systole can be valued upon the reduction or the increase of the pulse rate.

This is true not only for the healthy, but invariably for each heart. No matter whether we have to deal with a normal pulse rate, or the action of the heart be accelerated as is found in children and decompensated states, or whether we are dealing with the bradycardia of a vagotonic, in every case the time of action appears reduced corresponding with the lower pulse rate, and is prolonged during work.

Special mention should be made of the fact that where there is a fluctuation in the duration of the entire heart cycle, either in the harmless respiratory arrhythmia or in the pulsus irregularis perpetuus, the absolute duration of the systole is always just about the same and does not follow the fluctuation to which, therefore, only the diastole is subject. In such cases it is necessary to calculate the proportionate duration of the systole, the real time of action, from the average of as great a number of heart beats as possible.

A few examples may serve for illustration of the conditions described.

TABLE I.—PULSE RATE AND TIME OF ACTION.

Name.	Age.	Condition.	Curve.	Pulse rate.	Time of action, per cent.
L. K. . . .	26	Healthy	Normal	68	32.13
			Sleeping	58	31.65
			Working	96	39.55
F. B. . . .	34	Healthy	Normal	89	43.18
			Resting	75	40.82
			Working	102	49.22
H. T. . . .	35	Mitral and aortic insufficiency	Normal	92	49.04
			Sleeping	86	47.06
			Working	99	48.42
W. T. . . .	55	Arrhythmia perpetua	Normal	98	39.50
			Sleeping	74	32.99
			Working	110	43.66

It must be mentioned that, as regards time of action, there are no differences between the sleepless rest which is free from psychic excitement, and the real sleep. The only standard factor is, in both conditions, the number of pulse beats. Uneasy sleep with increased pulse rate, accordingly, exhibits an increased proportionate duration of the systole. A sixteen-year-old boy, who in the usual day curve in connection with 83 pulse beats had a time of action of 40.72 per cent, showed in the sleeping curve because of a tormenting, exciting dream a frequency of 104 beats and a time of action of 49.71 per cent! As such occurrences are comparatively

rare, we may say that during sleep both pulse rate and time of action are reduced.

If the time of action in the normal condition and that during rest be calculated on the basis of twenty-four hours and the results be compared with one another, then we find for the rest in two of the examined cases a shortening of only fifteen minutes; this reduction amounts in general to about thirty to forty-five minutes and has its maximum in a work saving of one and a half to two hours. Given a night's rest of eight hours and not too hard work during the day, the time of action of a healthy adult heart with a proportionate duration of the systole of about 33.5 per cent on the normal curve would be not eight hours, but about seven and seventy-five-hundredth hours. It must, however, be borne in mind that the resting and sleeping curves were already all taken after one hour and a half; in a continuously recumbent position of seven to eight hours' duration during the night or in rest in bed of several days the pulse rate and, accordingly, also the time of action often undergoes a more considerable diminution, so that then the heart may rest daily about one and a half to two hours longer than it usually does.

Influence upon the Pulse Rate. Our opinion coincides with the results of Klewitz's[3] researches on the pulse rate during sleep, according to which the reduction in the pulse rate is greater during the night's sleep than during the day's sleep. The difference is, of course, very low: On the average about 1.6 beats per minute. According to Klewitz, the average pulse reduction during the night is 14.8 beats; for the day's sleep the writer has found a reduction of 13.2 beats, as the following table demonstrates:

TABLE II.—INFLUENCE OF SLEEP ON PULSE RATE.

Age.	Diagnosis.	Normal pulse.	Pulse during sleep.	Difference.
24	Bradycardia	50	48	2
26	Healthy	68	58	10
25	Drop heart	68	62	6
34	Healthy	89	75	14
12	Tachycardia	128	92	36
35	Mitral insufficiency	92	86	6
41	Hysteria	99	71	28
23	Mitral insufficiency	71	69	2
37	Mitral stenosis	84	75	9
24	Tachycardia	141	133	8
55	Arrhythmia perpetua	98	74	24
Average				13.2

As we see, the maximum value for the reduction of the pulse rate by rest in day time is 36, the minimum value is 2 beats per minute. That restless sleep may cause an increase of the pulse rate, has been mentioned above.

As Klewitz already demonstrated, there are, referring to this,

no differences between healthy and decompensated hearts, while in a case of decompensation in a man, aged seventy-six years, with a totally allodromic electrocardiogram and a frequency of 144 beats rest which, it is true, was interrupted by coughing spells, did not result in a reduction of the pulse.

The increase in the pulse rate after work may also be illustrated by a series of examples.

TABLE III.—INFLUENCE OF WORK ON PULSE RATE.

Age.	Diagnosis.	Normal rate.	Rate during work.	Difference.
26	Healthy	68	96	28
25	Drop heart	68	73	5
34	Healthy	89	102	13
35	Mitral insufficiency	92	99	7
15	Healthy	74	79	5
48	Mitral insufficiency	69	80	11
31	Neuralgia	75	82	7
20	Healthy	56	64	8
23	Mitral insufficiency	71	81	10
52	Mitral insufficiency	56	62	6
37	Mitral stenosis	84	88	4
55	Arrhythmia perpetua	72	84	12
57	Arteriosclerosis	98	110	12
Average				9.8

Hence, work causes an increase of about 10 beats per minute in the pulse rate. Under work is understood the exertion described above, and it is natural that continuous labor yields higher values than those given here.

Influence upon the Time of Electric Stimulation. In addition to the finding that rest and sleep cause a reduction, work an increase of pulse rate and time of action, we observed as a second important result of the investigations a regular alteration of the relation between the time of action on the one hand and the proportionate time of electric stimulation on the other hand. Brugsch and Blumenfeldt[4] were the first to elaborate in a systematic way the comparison between ventricular electrogram and ventricular phonogram, a comparison which has also been studied by the writer in normal and pathological films.

The result of the comparison was that *during work the ventricular electrogram is always longer, and during rest and sleep always shorter than the ventricular phonogram.*

In the healthy adult where the difference between the two is equal to, or almost equal to zero, it becomes negative during rest and positive during work. If the difference is *a priori* quite high in favor of the electrogram, as is the case in younger years or in pathologic heart conditions, it sinks—remaining positive—considerably during rest and climbs during work.

TABLE IV.—EFFECT OF REST AND SLEEP ON RELATION OF VENTRICULAR ELECTROGRAM TO PHONOGRAM.

Age.	Diagnosis.	Normal relation, per cent.	Relation during rest, per cent.	Difference, per cent.
34	Healthy	0	−2.100	2.100
20	Healthy	0	−0.920	0.920
23	Mitral insufficiency	0	−1.440	1.440
41	Hysteria	0.140	−0.890	1.030
24	Bradycardia	0.430	−0.950	1.380
16	Lymphatism	0.660	−0.287	0.947
12	Tachycardia	0.885	−1.047	1.932
48	Mitral insufficiency	1.320	0	1.320
26	Healthy	1.356	−1.670	3.026
25	Drop heart	1.827	−2.470	4.297
15	Healthy	4.710	0	4.710
31	Neuralgia	5.230	1.610	3.620
52	Mitral insufficiency	6.640	5.990	0.650
55	Arrhythmia perpetua	6.830	5.150	1.680
57	Arteriosclerosis	7.750	2.300	5.450
37	Mitral stenosis	10.680	4.950	5.730
14	Tachycardia	16.120	8.020	8.100
76	Hypostatic pneumonia	14.500	9.000	5.500
	Average			3.000

The minus sign − indicates the shorter duration of the electrogram.

TABLE V.—EFFECT OF WORK ON RELATION OF VENTRICULAR ELECTROGRAM TO PHONOGRAM.

Age.	Diagnosis.	Normal relation, per cent.	Relation during work, per cent.	Difference, per cent.
34	Healthy	0	1.77	1.770
20	Healthy	0	1.03	1.030
20	Mitral insufficiency	0	0.56	0.560
41	Hysteria	0.140	1.17	1.030
24	Bradycardia	0.430	1.26	0.830
16	Lymphatism	0.660	0.75	0.090
12	Tachycardia	0.885	1.99	1.105
48	Mitral insufficiency	1.320	3.46	2.140
26	Healthy	1.356	5.77	4.414
25	Drop heart	1.827	1.88	0.053
55	Arrhythmia perpetua	6.830	9.78	2.950
52	Mitral insufficiency	6.640	6.76	0.120
76	Hypostatic pneumonia	14.500	22.00	7.500
	Average			1.800

From the two last tables it appears that the shortening of the electrogram when compared with the phonogram, amounts to an average of 3 per cent up to a maximum of 8 per cent, its prolongation after work to an average of 1.8 per cent up to a maximal 7.5 per cent. In other words, a dissociation is being produced between the duration of the mechanical action and the time of the electric stimulation of the ventricles under the influence of work in favor of the ventricular electrogram, but under the influence of rest, at its cost.

It is striking that the nature and height of said dissociation does not seem to have any direct relation to the pulse rate. In the above mentioned case of the man, aged seventy-six years, with a totally decompensated heart where the pulse in the normal, the resting and the working curves remained invariably at the same rate of 144 beats, there were, nevertheless, considerable differences in the time relation between ventricular electrogram and phonogram, namely, a shortening of 5.5 per cent at rest, a prolongation of 7.5 per cent at work, that is, an interval of full 13 per cent between rest and work. In a woman, aged thirty-one years, who, in the resting curve on account of intercurrent psychic emotions, had an increase of the pulse rate of 2 beats per minute compared with the normal curve, the ventricular electrogram was shortened at a rate of 3.62 per cent. In another case where, under the influence of a vagus stimulation immediately after work, the pulse rate had dropped from 50 to 45 beats, there was still a prolongation of the electrogram of 0.83 per cent, compared with the normal condition. Many more such examples could be cited. They all show that the regularity in the described relation between the time of electric stimulation and the time of mechanical action is not at all changed, even by alterations in the pulse rate.

It must further be noted that the stated prolongation of the time of electric stimulation after work outlasts the existing increase in the pulse rate for two to three minutes and, therefore, can still be elicited when the faster pulse has already slackened to the normal or has even reached a frequency lower than normal.

Thus, in each case, work causes a prolongation, rest and sleep a reduction of the time of electric stimulation of the ventricles, as compared with the time of mechanical action.

Influence upon the Time of Conduction. Another subject of the experiments was the time of conduction, that is the interval from the end of the auricular P wave to the beginning of the Q wave, during rest and work. The following table gives the results.

TABLE VI.—P-Q INTERVALS (TIME IN TWENTY-FOURTHS OF SECONDS).

P–Q normally.	P–Q during rest.	P–Q after work.
2.9	3.1	2.0
2.9	3.2	2.2
1.7	2.0	1.5
1.8	2.0	1.5
3.2	3.4	3.0
2.0	2.4	1.5
1.2	2.0	1.5

The table shows that the duration of the conduction of the electric stimulation through the bundle of His is absolutely prolonged during rest and absolutely shortened during and immediately after work. A great number of calculations have demonstrated that there is no

constant ratio governing the percentage relationship between the time of conduction on the one hand and the entire heart period or the duration of the diastole on the other hand. It was also interesting to find that in 1 case of pulsus irregularis perpetuus and auricular fibrillation with about 150 contractions of the auricles in a minute there was no change in the frequency of the auricular contractions though the original pulse rate of 98 went down to 74 during rest and up to 110 during work.

Influence upon Arrhythmias. The few cases of arrhythmias which were examined, demonstrated sufficiently that the irregularity as such always persists, but that in the condition of rest and sleep the difference between the single, prolonged heart periods becomes greater, while under the influence of work they appear to be about the same as on the usual day curve.

One illustrative example follows:

W. T., aged fifty-five years; pulsus irregularis perpetuus.

TABLE VII.—DURATION OF HEART PERIODS GIVEN IN ONE-TWENTY-FOURTHS SECONDS.

Usual condition.	Sleep.	Work.
10.0	12.6	20.2
15.0	30.2	13.2
13.0	16.5	13.4
13.6	10.1	8.6
11.4	22.6	16.4
16.2	19.0	8.2
17.6	14.9	10.6
9.2	21.4	15.5
16.0	11.0	8.3
16.5	36.0	16.2
Greatest difference 8.4/24	25.9/24	12.0/24

While under usual conditions and after work the longest difference in time between 2 of 10 heart beats on the table amounts to about half a second, it goes up during sleep to about twice as long a time, that is, to one second; this means that on the same resting or sleeping film of such a case one heart period may last one full second longer than another heart period.

We may mention here, too, that in 1 case, that of a woman, aged fifty-two years, whose extrasystoles had completely disappeared after prolonged medication with digitalis, the extrasystoles came back during the working experiment while they had not been present in the resting or in the usual curve.

Influence upon the Form of the Electrocardiogram. In order to study the influence of rest and work upon the form of the electrocardiographic waves, the writer had to eliminate the effect produced by the variations of the tension of the strings in that immediately before each of the three films (normal, resting, working) he gauged

the apparatus anew and kept the strings always at the same tension of 40 mm. Under such precautions, no difference, neither in the form nor in the amplitude of the single waves, could be found. The ventricular quotient $R-T$ had in each case a constant value for each of the three films.

Conclusions. 1. With the increased pulse rate after work there is a corresponding increased time of action; with the diminished pulse rate in the condition of waking rest and during sleep there is a corresponding diminished time of action.

2. Regarding time of action and time of electric stimulation, there is no difference between sleepless rest and sleep. Uneasy sleep with exciting dreams results in an increased pulse rate with prolonged time of action.

3. There is an alteration in the relation between the time of mechanical action and the time of electric stimulation under the influence of rest, sleep and work. During rest, the ventricular electrogram is shorter, after work longer than the ventricular phonogram. This prolongation of the ventricular electrogram after work outlasts the increase in the pulse rate for two to three minutes.

4. The time of conduction of the electric stimulation through the bundle of His is absolutely prolonged during rest, absolutely shortened after work. There is no law in its proportionate relation to the duration of the entire heart period or to the diastole.

5. In arrhythmias the difference in time between the single heart periods is increased during rest, diminished under the influence of work.

6. Extrasystoles which had disappeared after digitalis medication, reappeared during work.

7. Form and amplitude of the electrocardiographic waves remained unaltered.

8. Age, sex and blood pressure had no influence upon the conditions described.

BIBLIOGRAPHY.

1. Huerthle: Ueber die mechanische Registrierung der Herztoene, Pflüger's Arch., 1895, **60**, 263.

2. Brugsch and Blumenfeldt: Die Leistungszeit des Herzens, Berl. klin. Wchnschr., 1919, **40**, 937.

3. Klewitz: Der Puls im Schlaf, Deutsch. Arch. f. klin. Med., 1913, **112**, 38.

4. Brugsch and Blumenfeldt: Die Zeitunterschiede zwischen Elektrokardiogram und Kardiophonogram, Berl. klin. Wchnschr., 1919, **50**, 177.

THE POSITIVE CENTRIFUGAL VENOUS PULSE.

With a New Method for its Detection.

By William S. Middleton,
MADISON, WIS.

(From the Department of Medicine, University of Wisconsin.)

Tricuspid insufficiency of organic origin occurs very infrequently, but relative insufficiency of this valve is an almost inevitable consequence of cardiac decompensation of whatever source at some stage in its progression. Minor degrees of regurgitation doubtless occur under varying changes in the circulatory load as a result of the disadvantageous construction and support of the tricuspid valve; but it must be appreciated that any temporary advantage accruing to the right ventricle through this occurrence, is gained at the expense of the feeble right auricle and cannot be long sustained. This safety mechanism[1] to protect the right ventricle from overdistention has then distinct limitations. In this relation it is important to consider the position of the right ventricle in compensation. For all pulmonic lesions the load of circulatory imbalance is first met by the right ventricle. In all mitral lesions and in aortic lesions attended by relative mitral insufficiency the increased pressure in the pulmonic circuit is ultimately compensated for by primary hypertrophy of the right ventricle; and the final step in decompensation in left-sided heart lesions is dilatation of the right ventricle, leading to relative tricuspid insufficiency by one of two mechanisms. In some instances dilatation of the right ventricular wall operating through the papillary muscles and attached chordæ tendineæ on the free margins of the tricuspid valve eventually induces relative inadequacy in failing compensation. Or, depression of tone of the sphincter-like muscle fibers supporting the tricuspid ring may explain another group of relative insufficiencies.

The recognition of tricuspid regurgitation would, therefore, seem most important from a prognostic standpoint. The direct examination of the heart may reveal enlargement to the right. The complicating nature of relative tricuspid insufficiency explains the confusion of murmurs which commonly attends auscultation in these cases. Then, too, the weakened myocardium and the dilated tricuspid orifice are further mechanical reasons for lack of definition and absence of murmurs. Typically the murmur of tricuspid insufficiency is a soft, blowing systolic one, best heard at the xiphosternal junction to the left and transmitted up and to the right. Were the diagnosis of tricuspid insufficiency to rest on the examination of the heart alone, the majority of cases would pass unrecognized.

Since the influence of tricuspid regurgitation is reflected through distention of the right auricle back on the systemic venous return, venous engorgement, anasarca, albuminuria with reduced urinary output and more or less profound changes in the higher nervous functions dependent on disturbed circulation may be anticipated. As direct manifestations of these changes in the venous circulation, the positive centrifugal venous pulse in the jugulars and the pulsating liver have been held as practically diagnostic of tricuspid regurgitation by certain authorities.[2, 3]

Critical analyses of the venous pulse by graphic methods have failed to satisfy observers of the infallibility of its presence and significance. It is beyond the scope of the present consideration to discuss the interpretation of the phlebogram. Suffice it to state that Mackenzie[4] by clinical observations and Rihl[5] experimentally have established the fact that tricuspid regurgitation may occur without a positive venous pulse. Furthermore the ventricular form of venous pulse of Riegel[6] has been found to occur under other conditions than tricuspid insufficiency. Hewlett[7] gives three causes for the ventricular type of venous pulse, namely, simultaneous contraction of the auricles and the ventricles (as in heart block and extrasystoles), paralysis of the auricles and tricuspid insufficiency. Mackenzie[8] writes: "They have, therefore, regarded the ventricular form of the venous pulse as only a sign of tricuspid regurgitation, and have missed the real significance of this very important symptom. That it is a sign of tricuspid regurgitation there is no doubt, but it is a sign of far greater significance, namely, that the auricle does not precede the ventricle in the cardiac cycle." Vaquez[9] states that "contrary to the opinion of the older authors, examination of the venous circulation gives no indication whatever of the presence or absence of tricuspid insufficiency. It is to the disordered functioning of the auricle and not to the reflux of blood that we must attribute the phenomena of venous pulse and the ventricular form of the tracings."

Venous tracings are difficult to obtain and to interpret at times. Furthermore, much doubt has been cast on the pathognomonic significance of the ventricular form of venous pulse in tricuspid regurgitation by the above stated data. On the other hand study of the veins of the neck by direct inspection is frequently unsatisfactory by reason of the overactivity of the carotids. Furthermore, Vaquez[9] dismisses the importance of visible jugular pulse thus: "The sign that they thought almost pathognomonic was the systolic filling of the jugular vein after it had been emptied by pressure of the finger. Now, this sign which Potain also rejected, is of no value because it may be absent in undoubted tricuspid insufficiency and may exist in the absence of that lesion. It results not from the reflux of the blood through the tricuspid orifice, as was wrongly believed, but from the retrograde shock communicated by the

ventricular contraction to the column of blood retained in the auricle and in the jugular veins. The phenomenon of the venous pulse indicates that there is a stasis of blood in the auricle without prejudging the cause."

In cases of unquestionable tricuspid insufficiency, however, Osler and McCrae[3] report the presence of the regurgitant pulse wave not only in the jugular veins but also "in the subclavian and axillary veins and even in the subcutaneous veins over the shoulder, or in the superficial mammary veins." Mackenzie,[4] in addition to remarking like propagation of venous pulse waves, noted their presence in the small veins of the arm (twice) and in the veins of the face (once). He suggests the facilitation of these observations by the application of a thread of sealing wax to the skin overlying the vein, as suggested by King, or the sprinkling of pulverized glass mirror over the vein, after Czermak and Hippesley.

In the course of routine venous pressure studies of an individual seriously decompensated and showing a high venous pressure, a pulsation synchronous with the radial arterial pulse and centrifugal in direction was remarked in the superficial veins of the forearm and the dorsum of the hand. This venous pulse was exaggerated in expiration. This interesting observation led to a close scrutiny of the peripheral veins in all cases of cardiac decompensation and in certain types of compensated cardiac disease, as well as in a large control group.

The results which will be summarized shortly, were quite striking; and in the course of these studies an interesting and an apparently new factor in eliciting the centrifugal venous pulse was noted. The following case of cardiac decompensation with relative tricuspid insufficiency is quoted as presenting characteristic findings:

Case Report. W. B., aged sixty-nine years, presenting the classical picture of hypertension—myocarditis, is admitted in the third attack of cardiac decompensation. Dyspnea, swelling of the ankles and abdominal distention are his subjective complaints. Orthopnea, anasarca and cyanosis are established. A positive, centrifugal jugular pulse is suggested. Great numbers of coarse, moist rales are heard in both bases. A wavelike cardiac impulse is detected in the fourth and fifth left interspaces, anterior axillary line. No thrill is felt. The right and left cardiac borders in the second interspace are 38 and 30 mm.; in the third, 38 and 92 mm.; in the fourth, 51 and 150 mm.; in the fifth, 160 mm. (well into left axilla). The apical first sound is replaced by a loud blowing systolic murmur which is transmitted well to the axilla and the back. The pulmonic second is markedly accentuated. Softening of the aortic first sound with accentuation of the second is determined. The rhythm is regular. The vessels are tortuous and beaded. Blood pressure registers systolic 172 mm., diastolic 116 mm. The liver

extends 10 cm. below the costal margin in the right midclavicular line, but no expansile pulsation can be determined. Casts and albumin are present in the urine.

The venous pressure is 24 to 26 cm. of water. When the hand is elevated to a level 26.5 cm. above the midaxillary line (patient recumbent), a positive centrifugal pulse appears in the veins on the dorsum of the hand. Careful observation reveals no venous pulsation with the hand at a lower level and a sharp recurrence at the point of collapse of the vein. In the course of partial reëstablishment of compensation this phenomenon persisted without exception on daily examinations, until the venous pressure fell below 12 cm. fifteen days later. Its infallible appearance under the conditions stated was established many times.

In this case arterial hypertension and cardiac hypertrophy were apparent; and in addition there were unmistakable evidences of relative mitral insufficiency. Tricuspid insufficiency may be inferred from the jugular pulse, anasarca and hepatic congestion. The high venous pressure was suggestive of a damming back from the right heart. The appearance of a centrifugal venous pulse when the arm or hand was elevated to a level above the right auricle equivalent to the venous pressure, constituted a new observation in our experience.

In all, 14 cases showing clinical evidences of cardiac decompensation of such degree as to indicate probable right heart failure (comparable with (the case reported) have been studied with this point in view. Of this group 10 cases showed the centrifugal pulsation in the peripheral superficial veins of the forearm and hand, only when these parts under observation were elevated above the right auricle a distance equalling the venous pressure, or just before collapse of the vein was effected. At times it was difficult to judge whether the pulsation was more apparent at a point immediately below or just above that at which the veins collapsed; but as a rule the change was sharp and clear cut. In the remaining 4 cases centrifugal pulsation was noted in the superficial veins with the forearm on a level with the right auricle; but even in these cases the pulsation became perceptibly greater and clearer as the arm was elevated a distance equivalent to the venous pressure. Three of the 14 cases showing inferential evidence of tricuspid insufficiency and the positive centrifugal venous pulse have come to necropsy. In all of these cases, right-sided cardiac dilatation was marked. The measurements of the tricuspid valve were 12, 12 and 13.5 cm., respectively. The last figure alone is above the normal maximal figure; but the first two represent the upper limit of normal and for the female (as represented by the subjects) are possibly somewhat excessive. In any event stretching of the valve ring is not essential to a relative insufficiency and these cases unquestionably represent examples of

the mural myocardial stretch operating through the papillary muscles and the chordæ tendineæ to induce tricuspid insufficiency. In the surviving cases, a disappearance of the centrifugal venous pulse attended the reëstablishment of adequate compensation and the subsidence of signs of tricuspid incompetency. As a rule this point coincided with a venous pressure fall to 10 to 12 cm. but occasionally the venous pulse persisted with the venous pressure as low as 7 cm.

Control cases were studied to establish the possible appearance of this phenomenon in conditions other than those suggestive of tricuspid regurgitation. In no normal individual has it been observed, nor has it been seen in well-compensated cardiac lesions. No simple extrasystolic arrhythmia has shown the positive centrifugal venous pulse. Only 1 case of heart block has been available for study, and here again no such pulsation was remarked. In none of the 8 cases of fairly well compensated auricular fibrillation studied has this venous pulsation been noted. It has not been observed in any of 5 cases of pernicious anemia.

Elevation of the hand and forearm above the level of the heart apparently induces the simple hydraulic result of removing the inertia of a long column of blood in the veins of the arm, so that the relatively low pressure of blood thrown back into the auricle and the venous trunks by the right ventricle through the incompetent tricuspid valve may effect perceptible pulse waves. The small group of cases in which the regurgitant force was sufficient to produce the centrifugal pulse in the peripheral veins with the arm at the cardiac level and the improved visibility of even these waves on elevation of the part constitute evidences for the truth of the above explanation. In practice the radial vein is chosen for observation. A segment of this vessel is studied in an oblique light, the observer supporting the forearm and varying its level above and below the point of collapse of the vein. As a working basis the midaxillary line in the recumbent posture and the xiphosternal junction in the sitting or erect may be taken as the level of the right auricle. Visibility is improved by painting a small area of the skin overlying the vein with common aluminum paint. The direction of the wave is readily established by pressure on the vein above or below the point of study. Pressure proximal will obliterate the centrifugal venous pulse; distal, increases the same.

Conclusion. It is suggested that a simple procedure of elevating the arm may establish the presence of a positive centrifugal venous pulse in the radial vein in cases of relative tricuspid insufficiency and that this phenomenon is not observed in normal controls or in any of the conditions under which the ventricular type of venous pulse has been described, other than tricuspid insufficiency.

NOTE: Since submitting the proofs of this article, an admirable and exhaustive paper on the "Peripheral Pulsation in the Veins in Congestive Failure of the Heart" by William J. Kerr and S. L. Warren has appeared in the *Archives of Internal Medicine*, 1925, **36**, 593,

REFERENCES.

1. Sewall, H.: Safeguards of the Heartbeat, Am. J. Med. Sci., 1908, **136**, 32.
2. Norris, G. W. and Landis, H. R. M.: Diseases of the Chest and The Principles of Physical Diagnosis, Philadelphia and London, 1920, 2d edition.
3. Osler, Wm. and McCrae, Thomas: The Principles and Practice of Medicine, New York and London, 1920, 9th edition.
4. Mackenzie, Jas.: The Venous and Liver Pulses and Arrhythmic Contractions of the Cardiac Cavities, J. Path. and Bact., 1894, **2**, 84.
5. Rihl, J.: Ueber den Venenpuls nach experimenteller Läsion der Trikuspidalklappe, Verhandl. d. Kong. f. innere Med., Wiesbaden, 1907, **24**, 453.
6. Riegel, F.: Ueber den normalen und pathologischen Venenpuls, Deutsch. Arch. klin. Med., 1882, **31**, 26.
7. Hewlett, A. W.: On the Interpretation of the Positive Venous Pulse, J. Med. Res., 1908, **17**, 119.
8. Mackenzie, Jas.: Diseases of the Heart, London, 1918, 3d edition.
9. Vaquez, H.: Diseases of the Heart (Trans. Laidlow, G. F.), Philadelphia, 1924.

RAYNAUD'S DISEASE.[1]

LIMITATIONS OF THE CLASSICAL PICTURE AS A GUIDE TO DIAGNOSIS; REPORT OF A CASE SHOWING EXTENSIVE BONE INVOLVEMENT.

By James John Monahan, M.D., F.A.C.S.,

CHICAGO, ILL.

Much has been written since the days of Raynaud about the group of phenomena which now bears his name. In spite of this, however, how much have we actually added to our knowledge of this condition? Very little. Like Raynaud, we are compelled to reason to a vasomotor disturbance as the immediate cause of the gangrene, but as to the cause of this vasomotor disturbance, or its cure, we know as little as did Raynaud himself. One encouraging fact is to be noted, however. As more and more investigators have reported their observations, the term "Raynaud's disease" has come to include a wider and wider clinical picture. Under this heading we now find record of cases that have not advanced to a truly gangrenous stage, of gangrenes involving the deep as well as superficial structures, and of all manifestations of interference with the vasomotor mechanism in general, whether or not these were included in the original picture by Raynaud.

This modern tendency to extend the term Raynaud's disease beyond the classical picture has been noted by more than one medical writer, with approval by some, with disapproval by others. The suggestion has more than once been made that the term Raynaud's disease should be confined to the condition as described

[1] Read before the Faculty Clinical Meeting, St. Elizabeth's Hospital, Chicago, January, 1925.

by Raynaud, and that if one wishes to extend the picture another name had better be suggested.[2]

Regarding this we can only say that one's opinion thereon must be determined in a large measure by his opinion on the extension of eponyms in general. The question is an open one. To the writer it seems that this modern habit of ticketing with different names various phenomena which time and investigation have shown to be but different manifestations of the same affection is one of the great stumbling-blocks in the medical profession. Better the wider application of a name already established (even though it be an eponym) than the introduction of a new term which places the subject under a new heading in the various medical indexes. It is, therefore, with a two-fold purpose that the present paper is undertaken; first, to urge the further extension of the term Raynaud's disease to include all gangrenes, moist or dry, symmetrical or asymmetrical, deep or superficial, which give evidence of being due to defective vasomotor influence (as Raynaud himself undoubtedly meant it to include); second, to record a case of Raynaud's disease which the writer believes to be unique in both its symptomatology and its postoperative findings, and which was instrumental in calling to the writer's attention the fact that Raynaud's disease is not always attended by the classic Raynaud phenomena.

With Raynaud's original thesis on "Local Asphyxia and Symmetrical Gangrene of the Extremities" (1862) most readers are familiar. It was his purpose "to demonstrate that there is a kind of dry gangrene affecting the extremities which it is impossible to explain by vascular obliteration," and he hoped to prove that "this kind of gangrene has its cause in a vice of innervation of the capillary vessels." Regarding symptoms, he says, "The commencement takes place in different ways. In one case the extremities become pale, exsanguine, and then take on a lilac tint; tinglings or shooting pains occur—accompanied by numbness, but are soon replaced by burning heat; changes of color take place, violet becomes more pronounced—Area icy cold. Sometimes a livid redness first appears—Livid marblings show themselves in the neighborhood of the affected parts, and rise to a great height over the corresponding limbs. The digits may become entirely black, small phlyctenulæ may appear first on one digit then another, which break and leave the derma naked; all the nails may fall. Sloughs are formed. Parchment-like appearance may supervene without the blisters. Skin takes on a drab color, dries up, and a conical form of the finger ensues. Desquamation follows and thickened particles of wooden hardness are raised up in shreds." Much more might be quoted

[2] A principle concurred in by the Editor: In the present instances, however, the inclusion of cases that fall within his basic thought of gangrene due to defective vasomotor mechanism seems proper, at least for such variations as Raynaud himself includes and without resorting to a *reductio ad absurdum*.

along the same line, but this is sufficient to show the wide variation of symptoms as observed by Raynaud.

It is the chief criticism of those who deplore the freedom with which obscure gangrenes are diagnosed as Raynaud's disease that modern investigators are introducing new features into the picture and obscuring some of the old ones. But what are the features of the classic picture of this disease—that is, the *essential* features—which modern investigators have obscured? What are the essential features of Raynaud's disease, anyway? Are they to be identified with a host of "symptoms" which even Raynaud, with his limited sources of data, found so variable? No one symptom or phenomenon of a disease can be considered an essential feature of a disease unless it be a constant factor, and no one of the phenomena described by Raynaud has shown itself to be a constant factor in all cases of Raynaud's disease—a fact which should amply justify modern medicine in extending the clinical picture until some constant factor shall finally be found.

The objection might here be raised that blackness and dryness were both constant factors in the cases reported by Raynaud—that it was "dry gangrene" which he especially set out to explain. This is partially true, for Raynaud designated the gangrene under his observation "dry." That the cases themselves did not always conform to this description, however, is indicated by his mention of those having "small phlyctenulæ, which fill with seropurulent liquid." The same is true of color, which Raynaud described in a general way as "black." In the cases recorded the blackness shows great variation, ranging all the way from "a marked violet color which finally disappeared to "a color as black as that produced by burns of the sixth degree." To me it appears that both these features of the disease as described by Raynaud were more accidental than essential and that, having so little else to guide him in selecting cases for study, he naturally hit upon those which showed these spectacular features. Raynaud was also inclined to regard symmetry as a very distinctive feature of the disease of which he wrote, yet this has been for some time recognized to be of only secondary importance. For the truly essential feature, or features, of Raynaud's disease, then—for the constant factors which shall finally point us on to the basic cause—we cannot look to the classic picture described by Raynaud, much as we may respect his scientific efforts.

Indeed, on going thoroughly into the recorded histories of this type of cases, one begins to wonder whether there is a single feature of Raynaud's disease, either as described by himself or later writers, that is not open to controversy as to its essentiality. A certain condition which one observer finds to obtain in the special case or cases under his observation may be totally lacking in the case of his fellow-worker. The conclusions at which one investigator

arrives may be wholly at variance with the conclusions of other equally careful and reliable investigators.

It needs but a brief survey of the literature on Raynaud's disease to demonstrate this. One writer reports his case of symmetrical gangrene as first manifested by a condition of local syncope or asphyxia, as did Raynaud. Another finds that instead of becoming cold and white, or blue, the case under his observation first became a fiery red. Again, the patient may show alternating syncope and asphyxia, as in the case herein reported, or even alternating asphyxia and active hyperemia, as in the case reported by Dr. Weber.

The mode of onset of the disease Raynaud described as sudden, lasting from only a few days to not more than a month, and the duration short. Osler also described the disease as beginning very suddenly and running an acute course to a rapid termination. Numerous others have found this item inconstant, the inception of the disease varying from an acute onset coming on almost instantaneously, as in the case reported by Hutchinson, to as long as four years, as reported by Hollis. A. H. Ferguson found that the disease was usually preceded by chronic symptoms. Its duration has varied from only a few weeks to several years. In some cases the disease has recurred year after year for an indeterminate period. In the case reported in this paper the onset of the disease was gradual, extending over a period of nine months before becoming acute, and the disease of long duration, covering a period of four years before amputation was finally submitted to. In the 67 cases reviewed by Buchanan the onset of the disease was "usually sudden, but sometimes gradual," and this elasticity of description becomes more and more necessary the more cases we consider.

The type of gangrene is not the same in all cases observed. "Dry gangrene," said Raynaud, and "dry gangrene" have echoed most of the recorders of these cases. But is dryness a necessary feature of Raynaud's disease? Absolutely, no! What law of anatomy or physiology can be invoked to establish the assumption that a gangrene due to vasomotor disturbance must of necessity be dry? I know of no type of vasomotor interference capable of producing dry gangrene that is not equally capable of producing moist gangrene under slightly varying conditions. Dry gangrene is the result of an interference with the efferent supply of blood, in which the anatomical area thus shut off will mummify if kept clean, and eventually be amputated by Nature at the terminals of the collateral vessels. Moist gangrene is produced when the efferent supply of blood is intact and the afferent blocked. These two types of circulatory interference give widely different clinical manifestations, but either may be due to a defective vasomotor mechanism. Raynaud's disease is, therefore, probably as often moist as dry, although the moist type has to date received little attention in medical literature. A limited number of cases have

been reported, however, such as that of Ferguson in which the gangrene was moist, and of Landry whose case showed "gangrene of both big toes, the right moist, the left more or less dry."

Regarding the areas involved, there is less difference of opinion among recent writers than between the earlier investigators and later ones. Raynaud considered the type of gangrene of which he wrote essentially a gangrene of superficial structures. Although he records cases where the phalanges were sloughed off at the joints he found no case in which the bone itself was involved. Osler describes the area subject to this disease as "limited to the terminal phalanges only." More recent writers report cases where the gangrene has involved much more extensive areas including the nose, ears, lips, gums, both hands, both feet, and even whole limbs. Deep structures as well as superficial have been affected, and bones have become atrophic, and even completely absorbed, without sloughing of the superficial tissues. In the writer's case almost the entire bony skeleton of the medial-anterior portion of the foot was destroyed, some of it being apparently absorbed, and some of it carried away in microscopic particles in a discharge which was found upon examination to be sterile. The external tissues finally became withered and dark, but, except for several blackened ulcers on the under and inner surfaces of the foot, the sloughing was done by the deep rather than the superficial structures.

The same wide difference of opinion is found to exist among medical men as to the predisposing and direct causes of this disease. To Raynaud a predisposing cause for this gangrenous condition seemed a logical necessity, and he attempted to find this cause in the age, sex and temperament of the individual affected. He considered heredity an important factor, and sexual excitation a very possible cause. On these points later investigators sharply disagree. Monro found that 8 per cent of the 180 cases he reviewed showed hereditary influence. "Family predispositions are not uncommon," says Osler. "Heredity plays no part," says Buchanan, which is the opinion of the majority of later writers.

So also with nationality. For many years it was considered that Raynaud's disease was especially a disease of the French and Hebrews—an opinion which is still held to some extent today, although the preponderance of opinion is now in the negative. "Raynaud's disease appears to be more common in England and France than in Germany. It is relatively more frequent among the Hebrews," writes Osler. In explanation of this he suggests that the fair-skinned peoples, having the most pronounced capillary circulation, would naturally best withstand Raynaud's disease. "Whole nations are pallid, others rubicund," he writes. "There is an antagonism between the amount of pigment and the degree of permanent distention of the vessels of the skin. The darker Teuton races have not nearly the same rich blood supply to the

hands and face as the fair Teutonic people." But if this be a predisposing cause for Raynaud's disease should not the negro be especially susceptible? Is he? Lee reports 3 cases of Raynaud's disease in the colored race, and there have doubtless been others; but it has not shown a marked preference for the members of this race.

The average age of the sufferers is a subject upon which there is a fair consensus of opinion, this being from twenty to thirty years in about 60 per cent of the cases recorded, although there is a general range of age from six weeks (Friedel) to eighty years. In this regard, however, it is to be noted that the diagnosis of Raynaud's disease in old people is extremely questionable and would have to be proven by tissue examination to establish that the case was not one of senile gangrene instead.

The temperament of the individual (which Raynaud considered of great importance) becomes a matter of less significance the more it is investigated. For every case showing the typical "neurotic" temperament described by Raynaud, there can be found one showing a normal balance. The same is true of the "previous condition of health," which has been so often remarked in medical literature to be "exceptionally good" in these cases. Investigation will show that this supposedly robust health of the victims of this disease is a myth in about 50 per cent of the cases on record. Diphtheria, pneumonia, jaundice, influenza, migraine, duodenal ulcer, tuberculosis, malaria, "intermittent fevers," ague, and syphilis, as well as numerous other diseases, all make their appearance in medical literature associated with that gangrenous phenomena known as Raynaud's disease. Even the exceptionally good health which Raynaud claimed for his cases becomes a matter for thought when we observe that heart and pulse irregularity were present in several of Raynaud's cases, of several others he says "the abdomen was hard and tumefied," several were habitually subject to venous stasis, and twice did he observe the disease associated with "a phlegmon of the neck, having for its point of departure the glands under the sternomastoid."

It is in the etiology of Raynaud's disease that we find the greatest difference of opinion. Syphilis is thought by some to be the true causal agent of Raynaud's disease, and some ten years ago this theory was widely held although it is not borne out by the usual blood reaction in these cases. While there are cases on record showing syphilis associated with the Raynaud phenomena, there are also a great number of cases giving negative histories for venereal disease and negative Wassermann tests. Indeed, so repeatedly is a negative Wassermann test found in these cases that one is led to wonder whether there may not be some relationship between such blood and Raynaud's disease itself. Does Raynaud's disease insure a negative Wassermann through some chemicophysiologic

process, or does syphilis immunize the tissues to whatever produces Raynaud's disease? The subject is worthy of thought. Syphilis is usually the first thought of the investigator of a case of Raynaud's disease and there are probably few of these cases today that are not tested out as thoroughly as possible for syphilis. Yet the percentage of positive Wassermann tests is markedly small. There are some cases giving a positive reaction, it is true, but the diagnosis of Raynaud's disease in such cases is open to question unless tissue examinations have been made, for the gangrene may be that of syphilis, and due to arteritis.

Malaria, defective glands, cold and exposure have all been suggested as the cause of Raynaud's disease. Lack of certain internal glandular secretions is regarded by some as the true cause. Improper food balance due to a shortage of vitamins, reacting on the general metabolic processes of the body, is also receiving serious consideration as a predisposing cause. Sexual excess and excitation are suggested as causes by several writers besides Raynaud himself, but this is a theory that is rapidly losing ground, as well it logically might. Not only do the histories of the recorded cases fail almost uniformly to bear out this theory of "sexual excess," but the average age of the sufferers (twenty to thirty years) is not an age most likely to feel the baleful effects of sexual excess even were this a fact, nor react unduly to sexual excitation. DeForest advances the theory that Raynaud's disease is due to a toxemia of some kind, and suggests copper as the toxic factor in several of his own cases, since these worked in copper. While the toxemia theory is not without argument, DeForest's paper on this subject loses much by the fact that in only 3 of the 17 cases he reports is the history given with sufficient detail to enable the reader to review the findings upon which the diagnosis of Raynaud's disease was based.

No one theory regarding the etiology of Raynaud's disease has caused more argument than that of malaria. While this is a theory often discussed in later literature, it is not a new one. It was one of the first theories advanced during the wave of investigation that followed the publication of Raynaud's original paper on symmetrical gangrene, and was for a time so well received that in 1899 Monro wrote, "The relationship which is now known to exist between malarial fever and Raynaud's disease was scarcely appreciated by Raynaud himself." This "known" relationship is not now so well known however. There are unquestionably many recorded cases of Raynaud's disease, especially among those from the Latin countries and our own southern states, that show evidence of malarial infection. There are cases on record in which the presence of malarial parasites has been demonstrated and which have been greatly improved by the use of quinin. But, on the other hand, there are unquestionably many other cases in which the patient had not and never had had malaria.

In view of this great difference of opinion regarding the symptomatology and etiology of Raynaud's disease, what are we to consider the truly essential features of this malady? Is there no common ground upon which all agree which may serve as the great essential of Raynaud's disease, according to which obscure gangrenes may be diagnosed and classified with some hope of progress toward determining the fundamental cause of this disease? Certainly the problem is merely complicated by confining modern investigators to a "classical picture," or by grouping under different names the basically similar gangrenes which do not conform in detail to this picture. Not only does this complication permit the inclusion under the heading "Raynaud's disease" of many gangrenes which, though not properly speaking Raynaud's disease, show the classic Raynaud phenomena; but it serves to classify under other heads many true cases of Raynaud's disease which fail to show the classic picture.

I think all who have read Raynaud's own researches must agree that to Raynaud himself the great essential feature of the gangrene he investigated lay not in its manifestations, but its mechanical cause. "A kind of gangrene which has its cause in a vice of innervation," he said, and it was this idea of a gangrene *due to a defective vasomotor mechanism* which was the basic thought behind his researches. It is this same idea of a gangrene due to vasomotor disturbance that should guide us in our diagnosis of Raynaud's disease today. Any gangrene which upon careful investigation is found not to be due to vascular obliteration, nor to organic disease, but which can be accounted for only by "innervation of the affected part" may be truly diagnosed Raynaud's disease, whether that gangrene be moist or dry, symmetrical or asymmetrical, involve only superficial tissues or the deep structures as well.

As to the cause of the innervation there are doubtless as many etiologic factors as in other nerve diseases. To discover which of these are truly causative factors is of course the problem at hand. But the problem of basic cause is not simplified by including as true causes all the predisposing conditions of this disease. Many of the theories of the etiology of Raynaud's disease, such as those of cold, exposure, trauma, and the like, deal with predisposing conditions rather than true causes. That these conditions are factors to be taken into account is true, but they are factors which set the stage for Raynaud's disease rather than produce it. It is essential that a clear distinction be drawn between these occasions for the onset of the Raynaud phenomena and the fundamental cause of this disease. Cancer is well known to develop by preference in some nonnormal portion of the body—some anatomical area weakened by too great activity, or by inactivity, or made especially susceptible by injury—but we know that the *cause* of the cancer lies deeper than these conditions. So with Raynaud's disease.

Any condition which interferes with the normal vasomotor activity of a given part may serve as the occasion for the development of Raynaud's disease, but the fundamental cause of this disease must be looked for elsewhere, probably in some constitutional abnormality or subnormality in the patient himself.

Of just what this abnormality or subnormality may consist is the great problem to be solved, but since no microörganisms nor disease-producing bacteria have yet been found in connection with Raynaud's disease, it seems highly probable that as a foundation for Raynaud's disease there exists some chemicophysiologic toxin, a conclusion strengthened by the complete sterility of the discharge from the diseased tissues in the case herein reported. Whether that toxin be the toxin of fatigue or of faulty metabolism, of overstimulated or understimulated glands, or of ill-balanced chemical elements we can only conjecture, for we know little of the toxins at best. But that some toxin is a causative agent, which manifests itself in some local area made especially susceptible by cold, injury, or any of the previously mentioned agencies, seems strongly indicated.

Following is the description of a case which the writer believes to be of unusual interest for several reasons: (1) Because it showed so few of the classic Raynaud phenomena and yet, being due to vasomotor disturbance, was unquestionably Raynaud's disease; (2) because parts of the bony skeleton of the foot were sloughed out in a discharge (corresponding no doubt to the "seropurulent liquid" mentioned by Raynaud), which was found upon examination to be *sterile;* (3) because postoperative dissection showed a remarkable adaptation of the crippled foot to the new demands made upon it by change in position for weight-bearing.

Case Record. The patient, a French Canadian woman aged twenty-six years, at the time of operation (disease had been in progress four years), was unmarried and a school teacher by occupation. Her chief complaint was a symmetrical gangrene involving the anterior half of the right foot internal to the third metatarsal, and the fourth toe of the left foot.

Her father and mother were still living and in good health with eight children in the family. There was no known history of constitutional disease. One aunt of the patient suffered badly from rheumatism.

The patient had had the ordinary diseases of childhood, but no malaria, typhoid or scarlet fever. Wassermann was negative. The patient states she was always in excellent health before this malady came on. She was not of a neurotic temperament, but very stolid. Her menses were always painful but regular. She has always lived a regular life, in a pleasant environment and has enjoyed her occupation.

Four years previous to the date of operation, the patient dropped a piece of ice on her foot, striking the second toe of the right foot. There was no abrasion. The toe became swollen and remained so for about a week. During that time it was painful, but the pain subsided with the swelling and the patient experienced no immediate trouble therefrom.

About three months subsequent to the injury pain developed in the right foot, centering around the second toe and radiating up the leg both fore

and aft. Pain did not subside when pressure was removed from the foot. There was no swelling at this time, but the toe was sometimes white and at other times red; pain was most severe when the toe was blanched.

This condition persisted for about four months, when the patient noticed that the pain and whiteness seemed to have spread to the great toe, which also became very painful; alternating local syncope and asphyxia developing concomitant with the pain. Later the asphyxia ceased; the great toe became white and cold and remained so.

It was approximately nine months after the initial injury that gangrene developed, and this developed not primarily in the second toe of the right foot, which had received the greatest previous injury, but in the great toe. It was at this time also that pain was first noted in the fourth toe of the left foot, which gave the same picture of alternating syncope and asphyxia before noted in the right foot.

The patient at this time consulted a surgeon who removed the right great toe. Following the operation a discharge began from the wound which suggested infection, but later bacteriologic examination of a similar discharge showed it to be free from pus cells and to consist only of serum and broken down detritus.

The wound healed gradually and was closed in about three months time. The pain, however, and the blanching of the second and third toes of the right foot and the fourth toe of the left foot continued with even greater severity. Almost a year after the removal of the right great toe gangrene developed on the internal border of the dorsum of the fourth toe of the left foot. This toe was then removed at its metatarsophalangeal articulation. The wound healed by primary union.

After the second operation the third toe of the left foot became painful, and alternating syncope and asphyxia set in. About four months after this the under surface of the right foot, opposite the distal heads of the first and second metatarsals, became swollen and almost unbearably painful. During the height of the swelling gangrene developed over this area. The tissues broke down and a great deal of fluid was discharged. An ulcer persisted for many months. The swelling gradually subsided and the ulcer finally healed. (End of second year.)

Increase in temperature of patient was not noted at any time.

About three months after the healing of the above-mentioned ulcer the foot became suddenly swollen and remained so for about three weeks. Pain was always present, which was no more severe at the time of the height of the swelling than before the swelling began. Gangrene developed over this area, and later another ulcer developed to the outside of the scar of the former one, about opposite the distal end of the second metatarsal. This gangrenous area broke down and a large quantity of fluid was discharged.

It was at this time that the patient first came on the writer's service. The abovementioned discharge was examined and found to be sterile and to contain fine granules of bone. A complete examination of the patient was made, including repeated serological tests. All laboratory findings were negative. Blood picture normal.

Physical Examination. The head, chest, cardiovascular system, and abdomen were negative and reflexes normal. The only positive findings were in the lower extremities.

The right foot was moderately swollen and the skin corrugated and of a brownish-gray color. A sinus about ½ inch in diameter, opposite the distal head of the second metatarsal, was noted. There was no evidence of active pus invasion, although a serous discharge was exuding from the sinus. An ulcer about the size of a half-dollar was present about the sinus. The second and third toes were blanched, cold, and swollen. There was

moderate retraction of these two toes. The third and fourth toes were moderately hypertrophied. The whole foot showed a tendency toward inversion, but the change in position and form of the foot was not comparable to that noted at time of operation two years later.

The left foot was apparently normal except for the absence of the fourth toe, although the patient complained of pain in the third toe.

Radiography of the right foot showed the following (Fig. 1): Absence of the great toe and the distal head of the first metatarsal; absence of the whole of the second metatarsal and atrophy of the proximal head of the first phalanx of the second toe, with absorption of calcium in the second and third toes; absence of the distal head of the third metatarsal and about one-quarter of its shaft, distally; moderate hypertrophy of the fourth and fifth metatarsals.

The left foot shows absence of the fourth toe and moderate absorption of the chalk from the distal head of the fourth metatarsal and the internal aspect of the fifth.

High amputation of the right foot was recommended, but was refused by the patient.

About ten months later the patient was seen by the writer at a time when the foot was enormously swollen and even more than usually painful. It was thought by the patient that the foot ought to be opened to let out pus. I refused to do so, however, since there was no fever and no constitional indication of active pus infection. Again high amputation was recommended but refused by the patient.

Within a few days a more extensive gangrenous area developed at the side of the second ulcer, and later on a great amount of serous material and granular substance was discharged through an ulcer in this area of gangrene. This ulcer remained open until operation was performed one year later (Fig. 2).

One year later a high amputation at the junction of the upper and middle thirds of the right leg was performed.

A second Roentgen ray picture (Fig. 3), made just before operation, revealed the progressive destruction of foot bones since the former picture, and change in general position of foot. The right foot shows almost entire destruction of bones of the medial-anterior portion of foot; absorption of phalangeal portions of fourth and fifth digits, and increase of calcium carbonate in the fourth and fifth metatarsals. Note also the changes in position of toes, their retraction, and the thickening of the superficial tissues of the foot as manifested by their heavy shadows in the Roentgen ray.

The left foot shows little change except in the loss of chalk in the fifth toe and the distal heads of the fourth and fifth metatarsals. Fig. 4 shows lateral view of right foot.

Externally the foot was much as it had been two years previous, except that it was more shrunken and darker. Two sinuses were present on the under surface of the foot, as were scars of other sinuses now healed.

The great difference in the right foot at time of operation and at time of examination two years previous lay in its conspicuous adaptation of form to function (Fig. 5). From the time the patient was first seen until the leg was amputated the patient had taken great care to dress the wound aseptically and antiseptically and had continued to attend to her duties as teacher. The weight had, of course, been transferred to the outer side of the foot. The foot had gradually changed its characteristics in response to the changed demands upon it and at time of operation it resembled a left foot more than a right one. In fact it looked like a left foot on a right leg. The little toe, having been forced to bear the weight usually resting on the great toe, had increased in size and assumed a more abducted position,

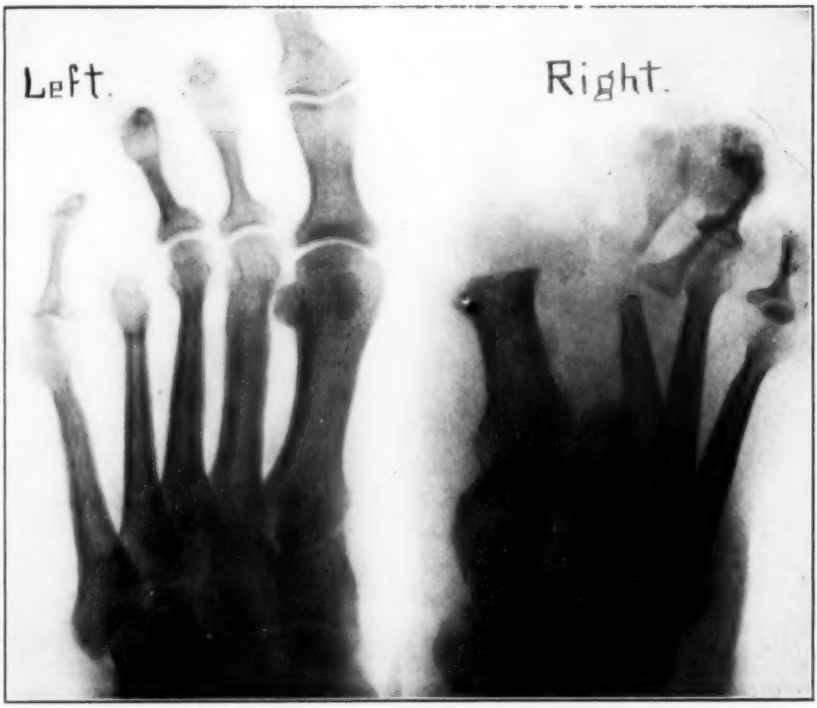

FIG. 1.—Roentgenographs of feet after Raynaud's disease had been in progress two years. Note: Right foot: Absence of great toe and distal head of first metatarsal (amputated); destruction by Raynaud's disease of the second metatarsal and proximal head of first phalanx of second toe; destruction of distal head of third metatarsal and about one-fourth of its shaft, distally; absorption of calcium carbonate in second and third toes; moderate hypertrophy of fourth and fifth metatarsals. Left foot: Absence of fourth toe (amputated) and foresigns of further extension of Raynaud's disease, as shown by absorption of chalk from distal head of fourth metatarsal and internal aspect of head of fifth.

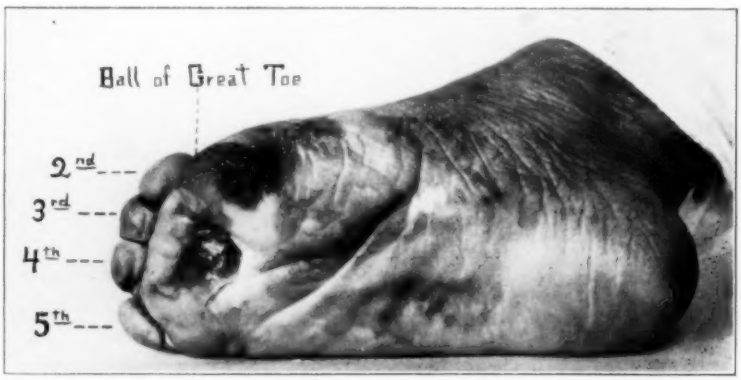

FIG. 2.—Right foot, plantar aspect, at time of operation.

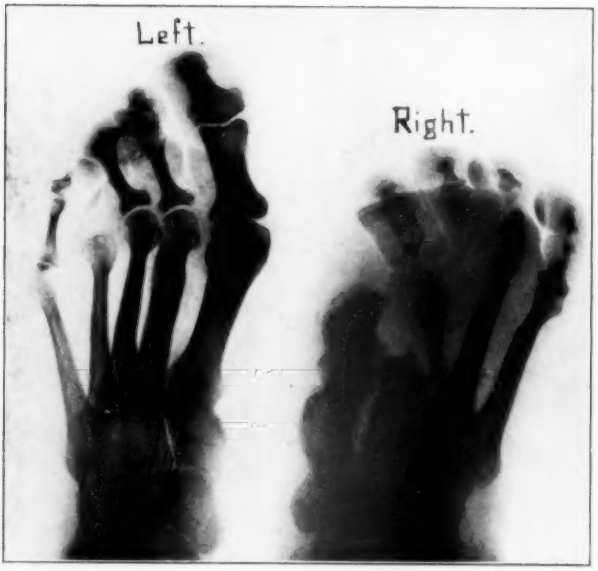

FIG. 3.—Roentgenograph taken two years after Fig. 1, showing progressive bone destruction. Note: Right foot: Entire destruction of bony skeleton of anterior-interior portion of foot; absorption of chalk from second, third and fourth toes; increase of chalk in fourth and fifth metatarsals; relative size of left and right foot; note also the abducted position and retraction of the second, third and fourth toes, and the denseness of the superficial tissues in the forepart of the right foot. Left foot: Further progress of Raynaud's disease over that shown in former roentgenograph is shown by absorption of chalk in the distal heads of the fourth and fifth metatarsals, the shaft of the fifth and the fifth toe.

FIG. 4.—Lateral view of right foot.

until it suggested the great toe itself. This likeness was further emphasized by the shrinking and retracting of the other three toes to allow the fifth one to become the predominating digit. So marked was this adaptation of the right foot that, shown at a clinic, it was unanimously voted a left one.

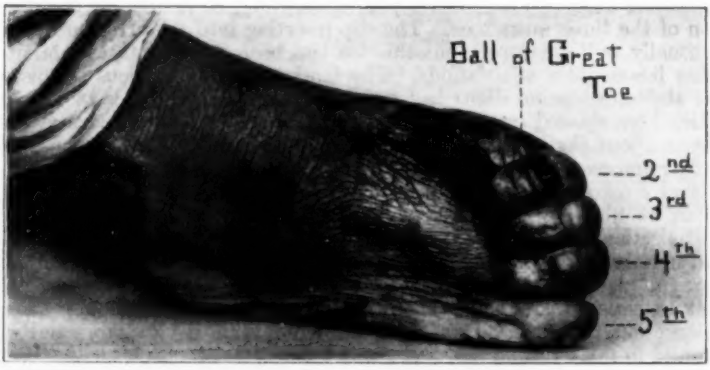

FIG. 5.—Right foot, dorsal aspect. Note change in relative development and position of toes, predominance of fifth toe and retraction and change of characteristics of the three inner toes, so that the fourth toe looks like a normal second and the second like a normal fourth. Adaptation of form to function.

FIG. 6.—Dissection of foot shown in Fig. 5, dorsal aspect. Note adaptation of ligamentous structures to new functions. *Extensor longus digitorum*, well developed; tendons of peroneus tertius and abductor minimi digiti fused with thickened, plantar fascia to form hammock-like sheath for fifth digit as aid in its new function of weight-bearing.

Likewise the other toes of the foot had changed their characteristics, so that the fourth toe looked like a normal second, and the second like a fourth.

Postoperative dissection showed further evidences of this adaptation of form to function in the development of the ligamentous structures of

the foot. In the under surface of the foot normal relationships were entirely destroyed in the medial-anterior portion, and it was impossible to identify the various muscles and tendons still remaining. In the dorsum of the foot, however, both muscles and ligaments were intact and showed marked compensatory development (Fig. 6). The tendons of the extensor longus digitorum were very well developed, accounting, no doubt, for the retraction of the three inner toes. The slip inserting into the fifth toe was also unusually well developed, but this toe had been saved from retraction by other ligamentous adaptations. The tendons of the peroneus tertius and the abductor minimi digiti had fused with the plantar fascia of the foot, which here showed marked thickening, and formed a strong, ligamentous sheath about the outer and under surfaces of the fifth digit, which apparently reinforced this digit for its new function as a great toe.

Such a marked adaptation in so short a time indicates a remarkable vitality in the undiseased portions of this foot, and is worthy of note.

Dissection also revealed important findings regarding the veins, arteries, and nerves. The bloodvessels were atrophied to such an extent that they were in places indiscernible, the atrophy being less marked the higher they extended up the leg. There were no evidences of venous or arterial obstruction. The nerves, on the other hand, seemed very large and were encased in fat.

Up to the present date (two years after operation) there has been no evidence of further disease of the right limb. For some months following operation patient complained of pain in the left foot, but this gradually subsided and she has had no further discomfort therefrom to date.

Summary. 1. Investigation of the basic cause of Raynaud's disease, and its cure, is hampered by the narrow limitations of the classical picture.

2. The guide to diagnosis of Raynaud's disease should be the evidence of defect in the vasomotor mechanism rather than conformity of clinical manifestations to the phenomena as described by Raynaud.

3. Thus, all gangrenes that can be accounted for by gross vascular obliteration, or other nonvasomotor causes, should be definitely excluded as "Raynaud's disease" even though they show the classic Raynaud phenomena; and, all gangrenes that give evidence of being due to vasomotor disturbance should be included as "Raynaud's disease," whether they be moist or dry, symmetrical or asymmetrical, involve only superficial tissues or the deep structures as well.

4. A chemicophysiological toxin is suggested as the cause of Raynaud's disease.

5. The record of a case of Raynaud's disease showing extensive bone involvement is of interest for several reasons: (1) Because it showed so few of the classic Raynaud phenomena and yet was unquestionably Raynaud's disease; (2) because parts of the bony skeleton of the foot were sloughed out in a discharge which was found to be sterile; (3) because of the remarkable adaptation of form to function displayed by the crippled foot.

A bibliography of the subject will be furnished on request.

THE RESPONSE OF THE NORMAL HUMAN STOMACH TO VARIOUS STANDARD FOODS AND A SUMMARY.

By Philip B. Hawk, M.D., Martin E. Rehfuss, M.D.,

and

Olaf Bergeim, M.D.,

Philadelphia.

(From the Laboratory of Physiologic Chemistry, Jefferson Medical College.)

In this communication we wish to summarize the results of the investigations which we have carried on for some years on the behavior of foods in the normal human stomach. While it is true that we have certain conceptions regarding the digestion of the various groups of foodstuffs, our knowledge on this subject has been largely based on Roentgen ray observations on the study of individuals with gastric fistulas, or otherwise traumatized, or by means of a method; namely, the old form of intubation, which did not permit of satisfactory study of the entire period of digestion. By recourse to fractional analysis we were able to follow the digestion of various foodstuffs throughout the entire period of gastric digestion and were enabled to study precisely the important points regarding their evolution. This series of studies, performed on a large number of normal persons, all of whom were completely habituated to the use of the tube, represents, to our knowledge, the first complete series of investigations covering the action of all the different varieties of foodstuffs in the normal human stomach. These experiments, extending over a period of six years, were performed under the best possible conditions and present a basis for the interpretation of pathological stomachs when examined under similar conditions. It was with this object in view; namely, to obtain an exact basis for the interpretation of pathologic data as well as to work out the exact influence of the various types of food in human digestion that this investigation was carried out. In this paper we wish to briefly point out some of the cardinal points in these investigations. In this series of studies, we examined, in connection with each foodstuff, the fast and slow stomachs which we recognized as variations in normal types. We also recorded the exact evacuation time of each particular foodstuff and the highest total acidity which was observed during digestion, and in many instances these studies were extended to include pepsin determination as well as formal titration. The quantities of foods were weighed and the chemical analyses were performed, in all instances, by chemists especially skilled in this work.

In a series of seventy complete experiments on twenty-five different subjects with 100 gm. of beef products which included

roast beef, rare, medium and well done; hamburg steak; sirloin steak; stewed beef; dried beef; tongue; corned beef; bologna; calves' liver; frankfurters; sweetbreads, and tripe; we obtained an average evacuation time of two hours and thirty-five minutes in the fast type of stomach and three hours and twenty-five minutes in individuals with the slow stomach. These gave a total average of approximately three hours for all varieties of beef products, and the average total acidity at the height of digestion for all forms of beef products was 120. It was interesting to note that roast beef appeared to be handled with practically the same ease whether rare, medium or well done, and no advantage was found in the evacuation of hamburg steak over the same weight of roast beef under identical conditions. Dried beef and corned beef presented similar reactions to roast beef. Tongue, however, was less readily digested than dried beef. In the study of the passage of meat from

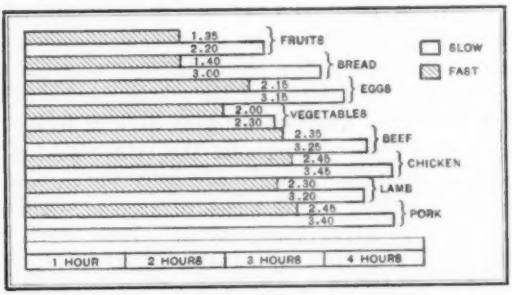

CHART I

the stomach into the duodenum, it was noted that there is a separation of the different parts of the meat which empty separately. The finely divided portions which settle to the bottom are affected first; this is followed by the coarse fibrous material and finally, the fatty material.

Thirty-one different tests on ten different subjects with pork products were made. These included roast pork; sausage; fried, boiled, minced and baked ham; bacon; liver and bacon; scrapple, and pork chops. In this group, the average evacuation time for rapid stomachs was two hours and forty-five minutes and for slow stomachs, three hours and forty minutes, showing a general average for pork products somewhat in excess of the period found with beef products. The average total acidity observed at the height of digestion was 117, while liver and bacon required about the same period of digestion as roast beef; pork chops and fried ham required a considerably longer period. Bacon alone required considerable time (four and a half hours) as compared with the average evacuation time of the rest of the food products.

Fourteen examinations were made of lamb products including roast lamb, stewed lamb, lamb chops and sheep's brains. In this group the average evacuation time for rapid stomachs was two and a half hours, and for slow stomachs, three hours and twenty minutes, showing a general average evacuation time similar to beef products; but the average total acidity was considerably higher; namely, 135 as compared with 120 for beef products. It is evident from this series that digestion of meat products generally, at least for 100 gm., is approximately in the neighborhood of three hours, and the highest total acidity in the neighborhood of 120, figures

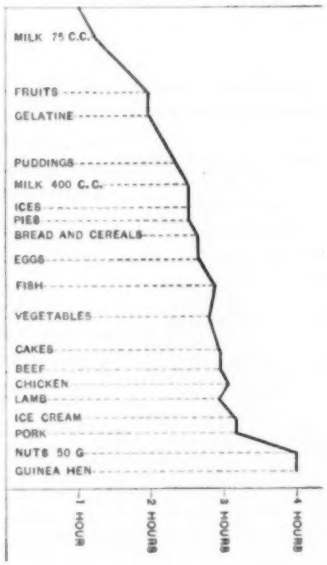

CHART II

which we have before pointed out as being construed by clinicians as high acidity.

Ninety experiments were performed on eighteen different subjects to test the response to eggs. Every variety of egg preparation was used including the raw white, the raw yolk, whole raw eggs soft boiled eggs, hard boiled eggs, scrambled eggs, fried eggs, plain and spanish omelet, deviled eggs, poached eggs, pickled eggs, duck's eggs, turkey's eggs, frozen hen's eggs, cold storage eggs and egg combinations such as milk and eggs, bacon and eggs, frizzled beef and scrambled eggs and the raw whites with orange juice. In each instance two eggs were used as an experimental meal, and it was noted that for all egg preparations the fast stomach showed an average evacuation of two hours and fifteen minutes, and the

slow stomach showed an average evacuation of three hours and five minutes, and for the whole series of egg preparations the average of the highest acidity was 80. Briefly, therefore, eggs give rise to less stimulation than meat and leave the stomach sooner, and show high combined acidities particularly through the early period of digestion. The raw egg white leaves the stomach more rapidly than any other form of egg preparation and produces only a moderate secretion of gastric juice in individuals of the hypersecretory type, a secretion which is only apparent toward the end of digestion. If distilled water is added to egg white, however, a more pronounced stimulation of secretion is produced. The egg yolk, on the other hand, produces a perceptible secretion and

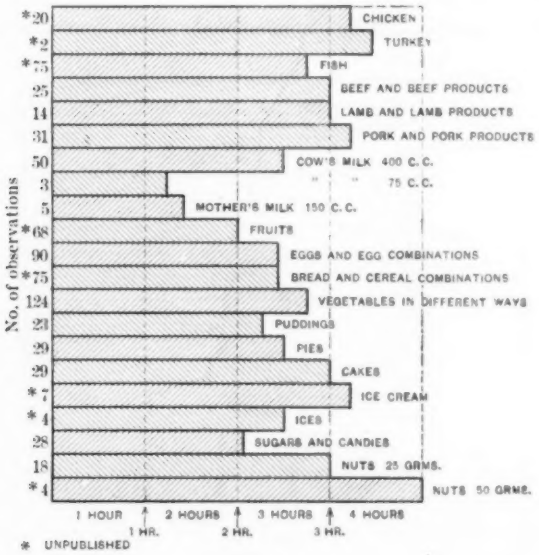

CHART III

requires a longer period for evacuation. For instance, in three subjects the average evacuation time for the raw white was one and a half hours, while in the same number of cases the average evacuation of the raw yolk was two hours and thirty-five minutes. Hard boiled eggs required only ten minutes longer in subjects of the rapid evacuation type than did soft boiled eggs. The average period for soft boiled eggs was two hours in rapid stomachs. In the same group, the average evacuation time for hard boiled eggs was two hours and ten minutes, while the acid response was similar in both. Fried eggs required only two hours and fifteen minutes. The eggs of the duck and turkey were handled in much the same way as hen's eggs. It is apparent, therefore, that eggs give rise

to a perceptible secretion even though it is less than that encountered with meat. Likewise a shorter evacuation period explains its value in many conditions associated with delayed evacuation.

One hundred and twenty-four experiments on thirty different kinds of vegetables were made on twenty-five normal men. The average evacuation time for all vegetables in the fast stomach was two hours and for the slow stomach, two and a half hours; while the average total acidity for the former was 70 and for the latter 77. This series included potatoes, (boiled, creamed, baked, mashed, fried) sweet potatoes, dasheen, cassava, oyster plant, beets, carrots, parsnips, radishes, turnips, beans, lentils, peas, asparagus, cabbage, coleslaw, sauerkraut, cauliflower, celery, lettuce, spinach, onions, cucumbers, squash, tomatoes, mushrooms, barley, rice, corn, hominy. The samples which were examined for fractional analysis were also examined microscopically with the view of determining the degree of disintegration and the extent of starch digestion and other changes. Vegetables fed in raw condition showed slow disintegration of the cells and cell masses. This was particularly noted for raw carrots, celery, tomatoes, lettuce, cabbage and cucumbers. Boiled carrots and cabbage showed much more complete disintegration, and this was true of most boiled vegetables; namely, white and sweet potatoes, turnips, squash, peas and dasheen. Somewhat less rapidly broken up were fried potatoes, spinach, string beans, oyster plant, parsnips, baked beans, asparagus, beets, sugar corn and cauliflower. The starchy vegetables such as potatoes were found to be considerably affected by salivary digestion. Sweet potatoes in whatever form remained longer in the stomach than white potatoes, and this was true of the dasheen. Oyster plant required the same period of time as white potatoes. Boiled beets and raw carrots left the stomach rather rapidly in from one to two hours while boiled carrots required a distinctly longer period. Radishes in small amounts left the stomach with great rapidity (one and a quarter to one and a half hours), while baked beans remained for a somewhat longer period in the stomach than most vegetables, requiring three and a half hours in the slow emptying type. Cabbage left rapidly as well as asparagus, asparagus leaving in one and a half hours, raw cabbage in one hour and forty minutes; and raw lettuce likewise showed an extremely rapid evacuation time of slightly over one hour. The addition of sugar, vinegar or oil, however, delayed the evacuation of lettuce. Spinach remained in the stomach distinctly longer than most vegetables. Raw tomatoes left earlier than boiled tomatoes. In two individuals with fast stomachs, raw tomatoes left in one hour and ten minutes, while the slow stomach handled them in one hour and fifty-five minutes. Canned stewed tomatoes, however, in the slow stomach required three hours. In general we noted that raw vegetables

which are low in protein such as carrots, celery, tomatoes, cabbage, lettuce and cucumbers left the stomach rapidly, developing moderately high acidities with but little combined acidities and left the stomach without great change in appearance. Boiled vegetables, however, showed much more rapid and complete disintegration. Furthermore, it is to be noted that vegetables high in starch such as potatoes may show in certain cases very considerable starch digestion before leaving the stomach so that the starch reaction is difficult to obtain.

Our results on milk are of particular interest. In these tests, we were fortunate in having the coöperation of a man who had the unique power of emptying his stomach completely at will or of giving small samples of the stomach contents at any desired stage of digestion. By making use of this man's skill as a regurgitator, we were able to demonstrate a number of things regarding the curdling and digestion of milk which would have been impossible without his aid. Brenneman[1] has also employed a regurgitator in the study of curd formation. However, his subject did not do "fractional" regurgitating.

Raw whole milk curded in rather hard, firm, white curds, possessing a rather rubber-like consistency. About one hour after the milk entered the stomach the maximum curd formation was noted. It was apparent that large curds were produced through the coalescing of smaller curds. At the one hour-period curds as large as a man's thumb and 15 gm. in weight were demonstrated. When the milk was boiled for five minutes the curds produced were yellow in color and small, soft and fine in appearance. From boiled milk the largest curds were no larger than a small pea. Curds of this character were more digestible than the raw milk curds and left the stomach sooner. Inasmuch as boiling for five minutes does not alter in any material way the nutritive or growth-promoting properties of the milk (except the antiscorbutic value which is lowered) it would seem that boiled milk should be given the dietetic preference. When raw skimmed milk entered the stomach, particularly tough, hard curds of large size were formed. The curd formation began in about a half minute and inside of five minutes the curds had coalesced to form individual curd masses as large as the thumb of a man. Our regurgitator complained of a heavy feeling in his stomach soon after drinking skimmed milk and had more difficulty in delivering samples of skim milk curds than curds of any other character. This was due to their firm, unyielding character. The curds from boiled skim milk were not as large and tough as were those from the raw skim milk nor as small and soft or as easy of digestion as those from the boiled whole milk.

[1] J. Am. Med. Assn., 1913, **60**, 575; Arch. Pediat., 1917, **34**, 81.

Inasmuch as the whole milk contained 4 per cent of fat, whereas the skim milk contained only about 0.5 per cent, it would seem that the character of the curd formed from boiled milk is regulated to a degree upon the quantity of fat present.

The influence of fat was also shown in our studies on cream. It was apparent in these tests that the character of the milk curds was influenced in a direct way by the fat content, that is, the more fat, the less curd. Furthermore, the curds were smaller and softer the higher the fat concentration. With 40 per cent cream, for example, no curds were formed during the first half hour. Moreover, the largest curds were only about the size of the head of a pin and they did not coalesce to form larger curds as they did with milk of low fat content. We also noted that milks of high fat value left the stomach slowly. In fact, 475 cc. of material was returned from the stomach two and a half hours after drinking 500 cc. of 40 per cent cream. An exception to the above rule was found in the case of skimmed milk (0.5 per cent fat) which left the stomach somewhat slower than raw whole milk (4 per cent fat). This finding was attributed to the fact that the curds of the skim milk were tough and disintegrated but slowly in the stomach.

When 2½ gm. of sodium bicarbonate was added to 500 cc. of raw whole milk, the curds produced were smaller and softer than were those formed in the absence of the bicarbonate. Curd formation began in about five minutes although the stomach contents were distinctly alkaline for a half hour. Boiled milk left the stomach sooner than the bicarbonate milk and the curds were smaller and softer.

The curds of pasteurized milk were found to be intermediate in character, between the curds of raw and boiled milk, with a tendency to resemble more closely the curds of raw milk. The pasteurized curds, however, did not coalesce to such an extent as did the raw milk curds.

If water was drunk before the ingestion of milk, there was no particular alteration in the curdling tendencies of the milk, except that the curds were somewhat softer and the maximum sized curds were smaller than when no water was taken. The extra volume of fluid in the stomach may have prevented the coalescing of small curds to form large ones.

Temperature had no material influence upon curd formation. Milks which were considerably below body temperature curdled a little more slowly but the delay was not conspicuous. We demonstrated that milks at 20° C. began to curdle in one to two and a half minutes, whereas milks at 37° C. began to curdle after the lapse of only a half minute.

When a mixture of 80 per cent boiled whole milk and 20 per cent raw whole milk was drunk the curds were similar to those obtained

from raw whole milk. The soft, fluffy, yellow curds of boiled milk were never in evidence.

The question of rapid and slow drinking of milk was also investigated. In these tests it was found that milk drunk rapidly left the stomach sooner and produced a smaller curd mass than did milk which was drunk slowly or sipped.

It was interesting to observe the response of the stomach to pies, cakes and puddings, and here again a study was made of the acid responses and evacuation time of nearly fifty different preparations. Twenty-nine experiments were performed on pies including pumpkin, mince, lemon meringue, raisin, coconut custard, cherry, peach, apple, and rhubarb. The findings in this series of cases were for the pie crust an average evacuation time of two hours and fifty-two minutes and for the inside of the pie two hours and twenty-six minutes. The average highest acidity developed with the pie crust was 90, while the average highest acidity for the contents was 103. Twenty-nine experiments were likewise performed on cakes including angel food, devil's food, fruit cake, lady fingers, crullers, doughnuts, cream puffs, short cake, cinnamon bun; and here again the average total acidity was 90 and the average evacuation time three hours and two minutes. Twenty-three experiments were performed on pudding including Indian, cornstarch, chocolate pudding, brown betty, cabinet pudding, rice, rice and raisin, cup custard, plum, bread, tapioca, and gelatin. The average total acidity was 92 and the average evacuation time two hours and eighteen minutes. Comparing the highest total acidities, therefore, for pudding, it was 92, for pie 90 and for cakes 90. Making a comparison of the type of food, it is evident that puddings are handled more readily than pies and cakes, the average evacuation of puddings being two hours and eighteen minutes, the average for pies, two hours and thirty-nine minutes and the average for cakes, three hours and two minutes. A number of interesting observations were made in this connection. Custard pies have a fairly high acid combining power, while the fruit pies have a low acid combining power. Angel's food cake remained distinctly longer in the stomach than devil's food cake and developed a higher total and combined acidity. Strawberry short cake left in from three to three and a quarter hours and developed a high acidity (127). The highest total in combined acidities was occasioned by Indian pudding, bread pudding and cup custard, all of which are high in protein. Gelatin, on the other hand, produced little acid stimulation and left the stomach rapidly.

A study was made also of sugars and candies, thirty-two experiments being performed with glucose, cane sugar, maple sugar, chocolate creams, chocolate, caramels, marshmallows, popcorn. In this connection, here again, it is evident that large amounts of

either cane sugar or glucose (100 gm.) markedly depress secretion and delay evacuation, while small amounts (10 gm.) do not appreciable affect either. It is for this reason that candies should be eaten after, rather than before, meals, but in any appreciable quantity they can delay the appearance of the secretion. Tables and curves summarizing our data on the motor and secretory activities of the normal stomach are reproduced herewith. The evacuation times and acidity values are given in round numbers in order to facilitate comparisons.

TABLE I.—MOTOR TABLE SHOWING EVACUATION TIME FOR VARIOUS ARTICLES OF DIET.

Article of diet (100-gram portions unless otherwise stated).	Number of observations.	Evacuation time (hours and minutes). Type of stomach.		
		Rapid emptying.	Slow emptying.	Average.
Beef and beef products	25	2.35	3.25	3.00
Lamb and lamb products	14	2.30	3.20	3.00
Veal:				
(*a*) Market	7	...	...	2.50
(*b*) "Bob"[1]	7	...	...	3.20
Pork and pork products	31	2.45	3.40	3.15
Chicken[1]	20	2.45	3.45	3.15
Turkey[1]	2	3.00	3.45	3.30
Guinea hen[1]	2	...	4.00	4.00
Fish[1]	75	...	...	2.50
Milk:[1]				
Cows':				
400 cc.	50	...	...	2.30
75 cc.	3	...	...	1.15
Mothers':				
150 cc.	5	...	...	1.40
225 cc.	2	...	...	2.25
Gelatin[1]	5	...	...	2.00
Egg and egg combinations	90	2.15	3.15	2.40
Vegetables prepared in different ways	24	2.00	2.30	2.50
Fruits[1]	68	1.35	2.20	2.00
Bread and cereals[1]	75	...	...	2.40
Cakes	29	...	...	3.00
Pies	29	...	...	2.30
Puddings	23	...	...	2.20
Sugars and candies	28	...	...	2.05
Ice cream[1]	7	...	...	3.15
Ices[1]	4	...	...	2.35
Nuts:[1]				
(*a*) 25 gm.	18	...	...	3.00
(*b*) 50 gm.	4	...	...	4.00

[1] Unpublished data.

The above are the complete tables up to date as about to be published by Rehfuss, Bergheim and Hawk.

TABLE II.—ACIDITY TABLE SHOWING HIGHEST TOTAL ACIDITY FOR VARIOUS ARTICLES OF DIET.

Articles of diet 100-gram portions unless otherwise stated.	Number of observations.	Highest total acidity (average) (cc. N/10 alkali to neutralize 100 cc. juice).
Beef and beef products	25	120.0
Lamb and lamb products	14	135.0
Veal:[1]		
(*a*) Market	7	140.0
(*b*) "Bob"	7	110.0
Pork and pork products	31	120.0
Chicken[1]	20	125.0
Turkey[1]	2	140.0
Guinea hen[1]	2	110.0
Fish[1]	75	130.0
Milk:[1]		
Cows':		
400 cc.	50	100.0
75 cc.	3	45.0
Mothers':		
150 cc.	5	60.0
225 cc.	2	90.0
Gelatin[1] (fruit juice preparations)	5	70.0
Egg and egg combinations	90	80.0
Vegetables prepared in different ways	124	75.0
Fruits[1]	68	90.0
Bread and cereals	75	80.0
Cakes	29	90.0
Pies	29	90.0
Puddings	23	90.0
Sugars and candies	28	70.0
Ice cream[1]	7	105.0
Ices[1]	4	65.0
Nuts[1] (25 to 50 gm.)	22	100.0

[1] Unpublished data.

The above are the complete tables up to date as about to be published by Rehfuss, Bergeim, and Hawk.

It is apparent from these studies that there are considerable gradations in both acid output and evacuation time with regard to even the separate groups. After this series of examinations was made it was suggested that we test the direct effect of emotion and psychic disturbance on individuals, and this we have attempted to do in rather an extensive fashion. In one individual who was about to undergo an examination in chemistry 100 gm. of fried chicken was tested out and the same quantity was again given after he was relieved of this strain. The emotional strain induced by an examination which he was uncertain of passing was sufficient to prolong, or rather retard, the digestion of chicken for over two hours and produce very high acidity. In a series of experiments on the effect of psychic influences, there was no question that the sight of a table which was properly laid out gave rise to a distinct secretion of gastric juice in normal individuals, while the sight of the same food, improperly prepared and poorly served, failed to give rise to an appetite secretion. Odor gave rise to less stimulation than the sight of food. Even the sound and thought of a frying steak gave rise to gastric secretion; however, it was to be noted that the ultimate utilization

of protein thus prepared in an unpalatable manner has not been found to be appreciably less than that of the same diet served under the best conditions. Anxiety and mental strain, however, will markedly retard gastric digestion.

Summary. In this series of studies, therefore, it is apparent that there is a certain characteristic response for each variety of foodstuff. The results also serve to emphasize the ability of the normal stomach to satisfactorily handle a great variety of foods. In each particular instance, the stomach has a certain amount of work to do which in health it does in a highly characteristic manner. The digestion of meats is one of great interest, and the same thing is true regarding the digestion of fresh vegetables. With the raw vegetables, however, digestion is much more of a mechanical procedure, but in each instance the test of a normal stomach is the ability of that stomach to handle these substances in characteristic fashion. Even in these experiments it was apparent that functional diseases almost always resulted in either a delay in evacuation or in a rise in the acid secretion or again in a failure of the stomach to react rapidly to the food in question. The exact significance of these findings we hope to work out in future experiments.

BIBLIOGRAPHY.

1. Bergeim, Ebbard, Rehfuss and Hawk: A Fractional Study of the Coagulation of Milk in the Human Stomach, Am. J. Physiol., 1919, **48**, 411.
2. Fishback, Smith, Bergeim, Lichtenthaeler, Rehfuss and Hawk: The Response of the Human Stomach to Beef and Beef Products, Am. J. Physiol., 1919, **49**, 174.
3. Smith, Fishback, Bergeim, Rehfuss and Hawk: The Response of the Stomach to Pork and Pork Products, Am. J. Physiol., 1919, **49**, 204.
4. Fishback, Smith, Bergeim, Rehfuss and Hawk: The Response of the Stomach to Lamb and Lamb Products, Am. J. Physiol., 1919, **49**, 222.
5. Miller, Fowler, Bergeim, Rehfuss and Hawk: The Normal Gastric Digestion of Eggs Prepared in Different Ways, Am. J. Physiol., 1919, **49**, 254.
6. Miller, Fowler, Bergeim, Rehfuss and Hawk: The Response of the Normal Human Stomach to Vegetables Prepared in Different Ways, Am. J. Physiol., 1920, **51**, 332.
7. Miller, Bergeim, Rehfuss and Hawk: The Influence of Tea, Coffee and Cocoa Upon Digestion, Am. J. Physiol., 1920, **52**, 28.
8. Miller, Fowler, Bergeim, Rehfuss and Hawk: The Response of the Human Stomach to Pies, Cakes and Puddings, Am. J. Physiol., 1920, **52**, 248.
9. Miller, Bergeim, Rehfuss and Hawk: The Influence of Sugars and Candies on the Gastric Secretion, Am. J. Physiol., 1920, 53, 65.

SOME REASONS FOR POOR RESULTS FOLLOWING GASTRO-INTESTINAL SURGERY.[1]

By Russell S. Boles, M.D.,

PHILADELPHIA.

There are many evidences in the literature that those who from time to time reëxamine patients after abdominal operations find the

[1] Read at a meeting of the Section of Gastroenterology and Proctology of the American Medical Association, May 29, 1925.

results of surgical intervention most disappointing. There is, furthermore, evidence in abundance to show that the reason operation fails to afford the patient symptomatic relief is that the fundamental cause of the trouble has not been discovered and removed.

Some time ago Rosenow[1] demonstrated the relationship between foci of infection, such as occur in the teeth and tonsils, and certain gastrointestinal lesions. An affinity was shown to exist between the organisms of such foci and alimentary structures—notably between the streptococcus and the gall bladder. Nakamura[2] has also shown experimentally that a distinct relation exists between certain foci of infection and ulcer of the stomach. This same relation appears to exist with lesions elsewhere in the gastrointestinal tract.

Although the exact relationship between disease changes in one section of the gastrointestinal system with those in another is not known, the feeling is growing that *isolated* lesions in any one organ rarely occur. Biliary disease, for instance, is invariably associated with disease in other viscera, especially in the liver, pancreas, appendix and colon. The association of hepatitis with chronic biliary disease and gastroenterocolitis has recently been vividly demonstrated by Heyd,[3] Stockton,[4] Tietze[5] and others. It is essential, therefore, from the etiologic standpoint, that we view the liver, pancreas, gall bladder and gastroduodenal segment as one physiologic and pathologic system.

In addition to infection, other etiologic factors that must be considered in effecting a cure in chronic gastrointestinal disease are visceroptosis, intestinal stasis, cecal dilatation, cecum mobile, asthenia, neurasthenia and familial predisposition, all of which are important predisposing conditions.

Appendicitis. A review of the literature of chronic appendicitis reveals a wide divergence of opinion regarding the nature, significance and treatment of that condition. Cabot[6] says he has *never yet* seen a patient whose symptoms he could attribute to chronic disease of the appendix. Among 15,000 cases of chronic dyspepsia he found that 12,600 owed their symptoms to extragastric lesions, but of these he does not consider chronic appendicitis as even a possibility. Mayo, Brewer, Deaver, Lichty and others, on the other hand, believe that chronic disease of the appendix is a frequent cause of gastrointestinal symptoms. There can be no question, however, that chronic appendicitis must often be considered an end result, and it must be determined whether the patient's symptoms may not be due to associated lesions, outside of the gastrointestinal tract, or to functional or systemic diseases that will continue to give symptoms after the appendix has been removed. Indifference to this fact unquestionably swells the already discouraging numbers of appendectomized patients who have secured no relief from their operation. Lichty,[7] for example, reports that of 517 patients sub-

mitted to surgery without any relief, 243 were operated upon for chronic appendicitis. Many of the surgical statistics present a lower percentage of failures, but this can be attributed to the fact that frequently the success of the operation was determined at the time of the patient's discharge from the hospital, and the cure at that time was more apparent than real. Deaver,[8] in speaking of the failures in a group of cases which he reports, says they were partly due to pathologic conditions, unrecognized because of faulty study and faulty exploration. Whiteford[9] writes: "Many patients whose abdominal ailments are now diagnosed as chronic appendicitis, suffer from symptoms of widely varying causation, and for these symptoms the appendix is not responsible." The symptoms attributed to the chronic appendix are not explained by the pathologic findings, and are not cured by removal of the appendix. Furthermore, the habit of attributing abdominal discomfort of obscure origin to the appendix hinders investigation into the causes of abdominal pain.

In considering the indications for operation the history and physical examination, and if accepted with caution the Roentgen ray evidence, serve as our best guides. Roentgenographic evidence alone, however, no matter how convincing, should never serve as an indication for operation. I think it may be conservatively stated that the mere procedure of removing the appendix will invariably fail to relieve the neurotic of his gastrointestinal symptoms, especially if he has a colitis, and the visceroptotic, particularly those with a mobile cecum and intestinal stasis, all of whom present a picture of chronic appendicitis.

The probabilities of cure from appendectomy—and, of course, acute appendicitis is not being considered—will be in direct proportion to the accuracy with which the occurrence of previous acute attacks can be determined. In summing up this question, Whiteford declares that: "In the interests of surgeons and patients the diagnosis of chronic inflammation of the appendix as a condition requiring operation should be abandoned."

Ulcer. While for the surgical treatment of peptic ulcer the percentage of failures may not be as great as that for chronic appendicitis, there nevertheless are many patients who should receive greater relief following operation than they do. Although statistics from reliable sources vary widely, they indicate that from 15 to 40 per cent of ulcer operations are failures. Excluding improper and imperfect surgery, which will not be discussed, the factors entering into the disappointing results are manifold. W. J. Mayo attributes 5 per cent of surgical failures in ulcer to faulty dietetics after operation. Inasmuch as most recurrences take place within two to three years after the operation, persistent adherence to medical treatment should be continued at least this long. Dr. Finney, a former President of the American Surgical Association,

struck a high note when he said: "Let us never forget that a surgeon's whole duty is not done when he sends a patient home with a healed wound. It is possible to have as an end result a perfectly healed wound with permanently impaired function."

Inasmuch as chronic ulcer of long standing has probably little tendency to heal and stay healed under medical management, the proper surgical treatment, provided adequate preoperative and postoperative attention is given the patient, should hold forth greater promise of ultimate cure. The surgeon's contention, however, that most ulcers even in their early stages should be treated surgically, is not borne out by the facts. The evidence tends rather to show that the recurrent character of the lesion depends on the formation of a new ulcer, or ulcers, and not, as a rule, on the breaking down of the old ulcer. The postoperative, as well as the medical, recurrence of ulcers suggests, as Smithies pointed out some years ago, that in treating ulcer one is dealing with only a local complication of a systemic or constitutional disturbance, to which must now be added a vital factor in the etiology of such disturbances, namely, infection. To our knowledge of the relation of focal infection as a cause of peptic ulcer, Hayden[10] has recently reported additional proof. Forty-five rabbits were injected with cultures from dental foci in 8 patients with peptic ulcer; 53 per cent of the animals developed peptic ulcer lesions, and the duodenal lesions were limited to the duodenal bulb just as they are in man. In view of facts such as these, it appears that the source of infection and the constitutional abnormalities should receive first attention. In connection with the latter, Devine[11] advances the conception that abnormal development or irritability or disease of the notoriously labile sympathetic nervous system can alter the postural tone of the gastric and duodenal muscle controlling the emptying time of the stomach, and the natural protective regurgitation which controls acidity, and may thus initiate a train of circumstances which may eventually result in ulcer. In addition to eradicating foci of infection, effective treatment of peptic ulcer must, therefore, be directed toward such underlying and predisposing conditions as nervous instability, overwork, worry, constipation and dietetic and other indiscretions. Recognition of these principles offers the only hope of an actual cure. It is plainly evident that the operation for gastric or duodenal ulcer must be regarded as only an incident in the treatment of the patient. As is the case with chronic appendicitis, cholecystitis, hepatitis and pancreatitis, ulcer is only an end result and, helpful as surgery is for this end result, the ultimate cure must depend on further enlightenment as to the cause and pathology of these ulcers.

Gall Bladder. In discussing the results following surgery on the biliary tract, we are again confronted with a formidable number of unimproved cases. Moynihan[12] reports that one-fifth of the

total number of patients suffering from cholelithiasis, upon whom he operated, had previously submitted to operation for this condition. Deaver[13] states that 4 to 8 per cent of patients operated on for biliary disease return because of recurrent symptoms; of these, 80 per cent have returned following cholecystostomy. Judd[14] reports, from the Mayo Clinic, that, during the year 1920, 1022 operations were performed on the gall bladder and ducts; of this number 114 were operations necessitated by the recurrence of symptoms after the first operations. In considering the etiology of disease of the biliary tract, first and foremost arises the question of infection, which we have already discussed, due emphasis being laid on the demonstrated affinity of the streptococcus for the gall bladder. The necessity, then, of tracing these organisms to their lair in the teeth, tonsils, sinuses, colon and elsewhere becomes apparent. Moynihan emphasizes the fact that a lurking area of infection anywhere in the body may be responsible for the recurrence of stones in the gall bladder, liver or ducts. He also attributes recurrence to an increased cholesterol content of the blood, and notes that 60 per cent of gall-stone patients are hypercholesterolemic, and in the remaining 40 per cent the blood cholesterol shows high normal values. Such findings have been confirmed by other investigators; there are, thus, strong indications that this substance may be the basic cause of the formation of these stones. Recognition of this factor is strictly essential in the preoperative and postoperative treatment of these cases if recurrences are to be avoided.

Once the gall bladder is infected, its early removal would seem to be indicated, in order to prevent secondary infection to adjacent organs. Judd considers it doubtful whether a gall bladder which has been extensively infected will ever function properly again. It must be remembered, however, that gall bladder disease is a disease of early life, and until we can be more assuredly convinced that this organ can be spared without harm, more conservative procedures are desirable. Early diagnosis is essential in any event. and it is earnestly to be hoped that the evidence secured by means of nonsurgical biliary drainage will soon offer us beyond any doubt more definite and dependable diagnostic data. As with appendicitis and peptic ulcer, the formation of gall stones might better be regarded as a terminal event. By the time they have formed, so much damage has been done to the associated organs that surgical and medical treatment are both heavily handicapped.

Preoperative and Postoperative Management. It may be unqualifiedly stated, I think, that biliary and intestinal stasis are, next to infection, and perhaps even ahead of it in importance, largely responsible in paving the way for the development of chronic gastrointestinal disease. This being the case, the whole subject of the management of these patients boils down to four leading essentials: (1) Eradication of foci of infection, especially in the

teeth, tonsils, sinuses, upper respiratory tract, appendix, gall bladder and colon; (2) elimination of intestinal stasis; (3) elimination of biliary stasis; (4) application of such measures as will improve the general condition of the patient.

The correction of intestinal stasis requires attention to diet and habits, general and abdominal exercises, abdominal supports, etc., none of which will be discussed at this time. I desire to give special emphasis to the value of drainage of the intestinal tract, which is just as essential, when indicated, as is biliary drainage. Transduodenal lavage, using the method of Jutte, also affords considerable relief in those cases of ileal stasis associated with colonic stasis.

By far the most satisfactory method of combating biliary stasis is by nonsurgical drainage. The writer has observed the effects of a large number of therapeutic biliary drainages, and in most instances decided benefit was secured. Lyon, Eggleston, Smithies, Niles, Umber and many others report beneficial results from nonsurgical drainage. According to Moynihan, the recurrence of stones after operation is frequently due to inadequate drainage of bile, that does not permit the escape of grit in the lower intrahepatic ducts and in the hepatic and common ducts. The practical importance of this method of treatment is therefore obvious.

In addition, such general and supportive measures are indicated as will strengthen the bodily resistance. There can be little question that a faulty or poorly balanced diet that is deficient in vitamins and such mineral substances as calcium, iodin and phosphorus must of necessity lead to general devitalization and lessen tissue resistance in the alimentary tract, which affords opportunity for bacterial invasion and subsequent disease. McCarrison's[15] work in this field is of particular interest. He spent nine years among the inhabitants of Himalaya, and performed on an average 400 major operations each year. During this time he was impressed with the infrequency of peptic ulcer, appendicitis and cholecystitis among these people. He attributes the freedom from those affections to their diet, the significant feature of which is the absence of white bread, potatoes, refined cereals, polished rice, sweets made of refined sugar and butter substitutes. McCarrison's suggestion, that one should eat one raw fruit, one uncooked vegetable, two green vegetables and 1 quart of milk daily, with a liberal supply of brown bread, butter, and only enough meat to supply the nutritional needs of the body, is of more than passing interest, and, if adopted, would unquestionably help in the prevention and treatment of alimentary disease. The consequences resulting from inadequate diet have been repeatedly proved by animal experimentation.

As long as one overlooks fundamentals in the management of these patients, and continues to make of them alkali addicts and

tube fiends, just so long one may not expect to reduce the number of operations performed on them, and the recurrence of symptoms after operation. The path of the chronic intestinal invalid is stormy, if not tempestuous; her comforts are meager; her miseries abundant. To our chagrin we not too seldom find that she has improved under the soothing and solicitous ministrations of the science healer or the confidently administered tomfoolery of the cultist. In any case they have secured for their patient a tranquillity of mind and a state of optimism and revived hope that we, either unknowingly or because of our inability, have failed to secure; such an accomplishment is frequently a key to a cure.

A note of caution may wisely be sounded in advising against indiscriminate surgery for chronic gastrointestinal disease. Surgery, however helpful, must in no sense be expected to secure complete relief for the patient. It is far from my intention to cast any shadow of doubt on the splendid and legitimate triumphs of modern abdominal surgery, but we must bear in mind that the performance of any operation that does not cure the patient of the ailment for which it was undertaken must needs bring surgery into disrepute, and arraign our medical profession before a jury of inquisitors of our wisdom.

Summary. Accumulating evidence reveals the fact that operations for chronic appendicitis, peptic ulcer and cholecystitis frequently fail to relieve the patient. The probable explanation of such failures is attempted, in which the etiology, the presence of multiple lesions in the gastrointestinal tract and other associated conditions leading to errors in diagnosis are discussed. Consideration is also given to the preoperative and postoperative management of such patients.

REFERENCES.

1. Rosenow: The Bacteriology of Ulcer of the Stomach and Duodenum in Man, J. Infect. Dis., 1915, **16**, 219; The Causation of Gastric and Duodenal Ulcer by Streptococci, J. Infect. Dis., 1916, **19**, 383.

2. Nakamura: A Study on Focal Infection and Elective Localization in Ulcer of the Stomach and Arthritis, Ann. Surg., 1924, **79**, 29.

3. Heyd, C. G.: Hepatitis, an Associated Condition with Gall-bladder Disease, Trans. Am. Gastroenterological Association, 1923; Surg., Gynec. and Obst., 1924, **39**, 66.

4. Stockton, C. G.: Gastrointestinal Infection of the Liver and Bile Passages, Am. J. Med. Sci., 1922, **163**, 485.

5. Tietze, A., and Winkler, K.: Participation of Liver in Gall-stone Disturbance, Arch. f. klin. Chir., 1924, **129**, 7.

6. Cabot, R.: Differential Diagnosis, 4th ed., vol. **1**.

7. Lichty: Relation of Cardiovascular Disease to Symptoms in the Abdomen, Atlantic Med. J., 1924, **27**, 419.

8. Deaver and Ravdin: End Results in 500 Cases of Chronic Appendicitis, Arch. Surg., 1923, **6**, 31.

9. Whiteford, H. C.: Chronic Appendix, Practitioner, 1922, **109**, 155.

10. Hayden, R. A., and Bohan, P. T.: Focal Infection in Peptic Ulcer, J. Am. Med. Assn., 1925, **92**, 409.

11. Devine, B. C.: Basic Principles and Supreme Difficulties in Gastric Surgery, Surg., Gynec. and Obst., 1925, **40**, 1.

12. Moynihan, Sir B.: Secondary Operations on the Biliary System, The Lancet, 1923, **2**, 4.
13. Deaver, J. B.: Some Surgical Relations of Cholecystitis, Ann. Surg., 1924, **79**, 726.
14. Judd, E. S.: Cholecystitis, with Special Reference to Recurrence of Symptoms following Operations upon the Gall Bladder, Journal-Lancet, 1921, **41**, 511.
15. McCarrison, R.: Studies in Deficiency Disease: Faulty Food in Relation to Gastrointestinal Disorders, J. Am. Med. Assn., 1922, **78**, 1.

THE PROPER CLASSIFICATION OF THE CEREBRAL PALSIES OF EARLY LIFE.*

By B. Sachs, M.D.,
NEW YORK.

As long ago as 1890 Dr. Peterson and I published a paper on the cerebral palsies of early life, in which we attempted to bring order out of chaos, and to establish what we thought was a proper clinical and pathologic arrangement of the spastic paralyses of childhood. Considering the relative frequency of these palsies and the serious effect they have on the entire development of the individual, it is strange that they should have held the attention of physicians less than almost any other order of disease, and yet they are responsible for the crippling of many an individual who might otherwise be equal to the average; the same causes which produce these palsies are also responsible for many of the cases of epilepsy and idiocy.

By "proper classification" I mean "proper interpretation" of these conditions from the clinical and pathologic point of view. During the past few decades important contributions have been made by Freud, Batten, Pierce-Clark, Ramsay Hunt and, very recently, by James Collier of London. A number of French and German writers have also been interested in the various subdivisions of the general subject.

The cerebral palsies of early life comprise a great variety of conditions, and any theory which would attempt to attribute all of them to any one cause could not possibly be correct. This is the cardinal difficulty with the attempt made by Collier to hold a primary degeneration of the cerebral neurons responsible for the development of all diplegias. To understand the subject at all, we must realize that this group comprises, clinically, all the diplegias and the paraplegias of early life as well as many odd forms of chorea, athetosis and the socalled choreiform or athetoid paralyses. We must also realize that while the first symptoms appear in the earliest months or years of life, some of them are evidently due to prenatal causes, others to difficulties during labor, while another

* Read before the New York Academy of Medicine, April 16, 1925.

and very important group are the acute or acquired palsies. While a very considerable number of the acquired palsies are hemiplegic in character, not a few are distinctly diplegic and some are paraplegic. All of these forms have certain features in common. The paralysis, whether it be a hemiplegia, a diplegia or a paraplegia, is invariably spastic. With it are associated, contractures and increase of all the deep reflexes in the parts involved; choreic, athetoid and associated movements of the paralyzed parts constitute a very characteristic feature of all these forms. Disturbances of sensation are unimportant. In the acute cases coma and convulsions may mark the onset, and convulsions may be so frequent as to imply a complicating epilepsy. Mental defects of varying degrees are developed in the course of years. The presence of spasticity and the entire absence of changes in the electrical reactions, the relatively slight atrophy of the muscles, help us easily to differentiate between the cerebral and the spinal palsies of early life. I need say little about the distribution of these cerebral palsies, except to note briefly that in a series of 225 cases which Peterson and I recorded, there were 81 right hemiplegias, 75 left hemiplegias, 39 diplegias and 30 paraplegias, and of the total, 134 were males and 91 females.

This general clinical division has been maintained throughout all the discussions, but other forms have been described. Clark has reported a series of cases which he has described as a cerebrocerebellar diplegia of flaccid, atonic type, and Ramsay Hunt has, very properly, segregated a series of cases under the heading of diataxia cerebralis infantilis. This ataxic type of cerebral birth palsies is characterized by "a generalized disturbance of coördination, involving the gait and station, the use of the arms and legs and the muscles subserving the function of speech. The incoordination persists in the recumbent position and has the characteristics of a true ataxia." There is neither paralysis nor spasticity, nor epilepsy nor serious mental defect. There will be little difficulty in accepting Hunt's type, as it will fit in very well with the general conception that clinical types of infantile cerebral palsy will vary in accordance with the distribution of the anatomic lesion. We all know that the hemiplegias are the expression of unilateral brain lesions, that the diplegias, double hemiplegias, can only be due to lesions in both halves of the brain, while the paraplegias may be due either to double brain lesions or, at least, to lesions affecting both pyramidal tracts. If the lesion involves the motor areas of both hemispheres, or the tracts immediately connected with them, we can readily understand the development of double hemiplegia. If the cerebellum be involved we may possibly be able to account for the types that Clark has described. Batten, by the way, has described a pure cerebellar type of diplegia. Foerster, in 1904, recorded an atonic astasic type, which he ascribed

to extensive lobar sclerosis of the frontal region, and Hunt believes, without definite anatomic evidence, as he himself states, that his type may be due to injury to the fetal head at birth, producing rupture or thrombosis of the cerebral veins with limitation of the lesions to the cortex of the parietal lobes. In this he approaches Gowers' concept of the importance of the meningeal veins in all these disorders. Hunt considers the diataxic form to be the sensory equivalent of cerebral diplegia and argues very correctly that the parietal lobe is the great receptive center for the registration of sensory stimuli. I hope that through some fortunate circumstance Hunt may be able to prove his theory to be entirely correct. It is plausible and entirely acceptable as a theory.

On clinical grounds there can be no objection to the establishment of a large number of types. Some confusion, however, has been produced by the fact that many authors have spoken of Little's disease as though it were a distinct clinical entity. The confusion was so great many years ago that, among others, I was led to ask, in 1897, "What is Little's disease? shall we retain the name?"

I stated that Little's disease is "whatever an author pleases to make it." Some of the facts may be rehearsed briefly: In 1862 Little published a very important paper on the influence of abnormal parturition, premature birth and asphyxia neonatorum, in which he showed that the spastic rigidities and the spastic palsies appearing early in life were due to protracted labor and premature delivery. German and French authors who took hold of this conception applied the term "Little's disease" to all early spastic rigidities and palsies, and this same custom has largely prevailed up to the present time, so that it has been the practice among many writers to speak of all congenital diplegias and paraplegias as Little's disease and, somewhat illogically, they have held that the etiologic factor which Little stipulated for the cases which he recorded was the universal cause of all these early spastic diplegias and paraplegias.

Used in this way, the name is an entire misnomer, for many reasons. First of all, we now definitely know that not all of the cerebral diplegias and paraplegias are due to difficulties at birth, or to premature delivery, and we also know that difficulties during labor produce hemiplegias as well as diplegias or paraplegias. If the name is to be used at all, it should be restricted entirely to forms of spastic paralysis, whether they be unilateral or bilateral, that can be definitely ascribed to difficulties during labor or to premature birth.

For all practical purposes it will be well to pay less attention to the exact form of the paralysis so long as we know it to be definitely cerebral and not spinal, and to group the various cases according to the time of onset and to the morbid lesions that have been definitely ascertained to be the prime cause of one or the other

forms of paralysis. Simple as this question of the morbid lesions would appear to be, the one great obstacle to a clear understanding of the subject is that in a large number of cases the lesions found represent terminal states, while every vestige of the primary pathologic process has disappeared. Another difficulty met with is that even though the first signs of paralysis may be evident several months after birth, or immediately at birth, such paralysis may be the expression of morbid processes beginning during the intrauterine period, or of imperfect development of the motor system.

The general classification which I presented in 1895 has met with the approval of many writers. Recent studies call for some modification.

CLASSIFICATION OF INFANTILE CEREBRAL PALSIES.

Groups.	Clinical forms in order of frequency.	Morbid lesion.
I. Paralyses of intrauterine onset	Diplegia, paraplegia, hemiplegia	Large cerebral defects (porencephaly); defective development of pyramidal tracts; agenesis corticalis (highest nerve elements involved); polioencephalitis (?); primary neuronal degeneration.
II. Birth palsies	Diplegia, paraplegia, hemiplegia, diataxia, cerebellar form	Meningeal hemorrhage, rarely intracerebral hemorrhage. Later conditions: Meningoencephalitis chronica; lobar sclerosis and cysts; partial atrophies.
III. Acute (acquired) palsies	Hemiplegia, paraplegia, diplegia, choreic and athetoid disorders (unilateral and bilateral)	Hemorrhage (meningeal and rarely intracerebral); thrombosis (from syphilitic endarteritis and in marantic conditions); embolism. Later conditions: Atrophy; cysts and sclerosis (diffuse and lobar); meningitis chronica; acute encephalitis (cortical and striatal); polioencephalitis acuta (Strümpell).

In the first group, the paralysis of intrauterine onset, we know that the paralysis may be due to large cerebral defects known as porencephaly, that there may be defective development of the pyramidal tracts, that in some cases there may be an *agenesis cerebralis* or a defective development of the highest nerve elements of the entire central nervous system. In some there may be, accepting Collier's designation, a primary neuronal degeneration. The occurrence of an intrauterine infectious encephalitis has been looked for, but not proved. Clinically, this group includes the cases of diplegia or paraplegia which may or may not be associated with choreic and athetoid movements. Some, in the course of years, develop marked mental defects; others, again, go through life with a fair mentality but with markedly disturbed motility.

There is the closest possible resemblance, clinically, between Groups I and II. The palsies of Group II are due to difficulties

during labor, to prolonged labor or instrumental delivery. First-born children are especially prone to these affections. The primary cause is a meningeal hemorrhage, rarely an intracerebral hemorrhage. The terminal conditions may be a chronic meningoencephalitis or a lobar sclerosis. In some instances cysts and partial atrophies are found.

I have said above that hemiplegias are sometimes due to difficulties during labor, so that there might be hemiplegias that could be construed as distinct birth palsies; but the diplegias and paraplegias have stood in the minds of many as the clinical representatives of true birth palsies or of paralysis due to intrauterine affections, or to developmental defects, and in this way much confusion has been created. This confusion has been increased by the recent article of James Collier who, in a Presidential address, delivered before the Neurologic Section of the Royal Society of Medicine, in October, 1923, has endeavored to maintain the proposition that all cerebral diplegias are due to disturbances in development, and has gone especially out of his way to show, so far as the group of birth palsies is concerned, that we have been misled all these years in attributing great importance to the communication of Dr. Sarah McNutt, in 1885, in which she showed that diffuse meningeal hemorrhage over one or both hemispheres at the time of birth is responsible for some of the cases of double infantile spastic hemiplegias.* I have gone over the original paper of Dr. McNutt on double infantile spastic hemiplegia, and can find no fault with her conclusions. In her case the child was the sixth in its family, and was delivered with instruments. Convulsions occurred during the first nine days of its life, with but short intermissions (very strong evidence of an irritative process). There was a spastic diplegia, cross-legged position and repeated epileptic seizures. Death from pneumonia occurred at the age of two and a half years. Amidon and W. H. Welch are sponsors for the pathologic findings, which show clearly a double well-localized active process leading to "atrophy of the paracentral lobule of the central convolution," and so forth, just where hemorrhage from application of forceps might have been expected. Welch's report disproves Collier's theory of a primary degenerative affair. Welch's diagnosis reads: "Sclerosis of the greater part of the motor cortical area in both hemispheres with secondary descending degeneration of the pyramidal tracts."

Collier insists that the morbid process was begun long before birth; he infers this from the primitive nature of the arrangement of the convolutions and from the condition of the pyramidal tracts.

* If proof were needed of the frequency of meningeal hemorrhage at birth, we might add on the authority of Peterson that Litzmann examined 161 stillborn children, finding in them 35 cases of meningeal hemorrhage; that Parrot in 34 autopsies on the newborn found 5 with blood in the arachnoid cavity and 26 with hemorrhage into the subarachnoid space.

Collier's argument is not at all convincing and, while it may not be correct to ascribe all cases of diplegia or hemiplegia appearing shortly after birth to natal hemorrhage, the evidence that such hemorrhages do occur is almost overwhelming, and there is no reason in the world to discard such evidence in favor of a theory which may be ingenious but not satisfying.

In seeking further proof of his theory, Collier refers to the fact that in amaurotic family idiocy there is a primary neuronic degeneration. He says that this origin has always been accepted, and it is his contention that this disease should be included among the diplegias. He also goes on to say that the disease is characterized by marked paralysis, sometimes there is optic defect and "sometimes no familial or racial incidence can be traced." The argument is faulty, and the facts are not stated carefully. The paralysis in many of these cases is only incidental, as I pointed out years ago. There is not a single case without optic defect, and if there ever was a disease in which there was distinct familial or racial incidence, it is this form of family affection; yet Collier bases his argument largely upon the primary neuronic degeneration occurring in this special form, which is not a typical diplegia. That many of the diplegias are related to hereditary and family disease I have at various times conceded, but there is no reason to ascribe all of these diplegias to this one cause. It is interesting in this connection to take note of van Gehuchten's theory, that the pyramidal tract reaches the medulla at the end of the seventh month of fetal life, and that this failure of development of the pyramidal tract would cause rigidity of the trunk and of all four limbs. In cases of premature birth at the end of the eighth month it has reached the dorsal region, and therefore premature birth at this time would cause rigidity of the lower limbs only. After birth the arrested growth is amended, and for this reason some of these cases tend to improve and sometimes to recover. The theory of primary neuronal degeneration may suffice as an explanation for some of the cases that we may, roughly speaking, ascribe to defective development of the central nervous system, but it can surely not be held to be the chief cause of all the cerebral diplegias.

Let me review, briefly, a few significant clinical facts. The palsies due to intrauterine disease or to arrested development, and those due to traumatism during labor give a distinct history of early onset of all the symptoms. Bilateral palsies are more common than in the acute cases, but the paralysis is not necessarily complete. At times it is a simple paresis; at other times rigidities and contractures are more prominent than are the palsies. Little made a sharp distinction between rigidities and palsies. In this he has been followed by some continental writers, but Freud, Peterson, Sachs and other American writers have maintained that rigidity, contracture, choreic or athetoid movements, paresis, uni-

lateral or bilateral, constitute a graduated series of disturbances due to cerebral lesions in children. Each or any one of these clinical manifestations may be present in a given case and may vary according to the site and intensity of the lesion. It is not uncommon to find that in cases of diplegia there may be paralysis in the lower extremities and athetosis in one or both upper extremities. Double athetosis is a condition closely analogous to double hemiplegia with less paralysis, however, than in the majority of other spastic palsies. The studies of encephalitis have convinced us that the choreic and athetoid movements are more apt to be present with lesions of the basal ganglia than in those involving chiefly the pyramidal tracts from the cortex downward. In other words, that they are apt to be due to extrapyramidal disease. Freud, who was one of the best students of this entire subject, found it necessary on purely clinical grounds to subdivide the diplegias into four groups: (1) Universal spastic rigidity; (2) paraplegic rigidity; (3) bilateral hemiplegia; (4) bilateral chorea and bilateral athetosis. I have no doubt that we shall be able soon to give the exact anatomic basis for these various clinical subdivisions. It is worth noting that Charcot, Marie, Déjerine and others insisted that congenital spastic paraplegia may be a spinal affection and due to defective development of the pyramidal tract. This may be true, but the high percentage of idiocy among children with congenital paraplegia leads to the inevitable conclusion that disease of the pyramidal tract alone cannot be held responsible for the entire group of symptoms observed in so many of these cases.

Many interesting questions arise in connection with the third group of cases—the acute (or acquired) cerebral palsies of children. Why do children develop these palsies? What are the points of resemblance and the points of difference between these acute palsies of early life and the typical apoplexies of the senile and presenile period?

There can be no doubt that hemorrhage, embolism and thrombosis, the conditions which give rise to the vast majority of apoplexies in the adult, are important factors in the causation of the acute cerebral palsies of children. In studies made many years ago by Osler, Peterson and myself it was found that in one series of 78 cases there was definite evidence of hemorrhage in 23, of embolism in 7 and of thrombosis in 5 cases. In 42 other cases terminal conditions were reported and these were more or less useless in helping us to ascertain the primary lesion. In Osler's series of 90 brains which he examined he reported a vascular lesion in only 16, of which 7 were due to hemorrhage and 9 to embolism. But, of course, a very large number of cystic conditions that were included in the Osler series may have been originally due to hemorrhage or embolism. The causes which lead to embolism and thrombosis in children may be inferred from the conditions in the adult pre-

disposing to these same vascular accidents. Some writers insist upon a greater frequency of embolism, others believe that hemorrhage is more frequent in children, while Gowers stood alone in maintaining that thrombosis of the superficial veins is a noteworthy initial lesion. Hunt has joined him in this. With regard to the occurrence of hemorrhage in children, it is fair to inquire what morbid condition of the bloodvessels in children would rank with the arteriosclerotic changes and the miliary aneurysms of the adult.

I gave a great deal of thought to this matter many years ago, and was relieved to find that von Recklinghausen, in his masterly monograph, stated that fatty degeneration of the bloodvessels in children is frequent, and may be accepted as a partial explanation of the occurrence of hemorrhages in the infantile and youthful brain. Steiner had expressed a similar view. I was also puzzled to discover why in the adult the majority of hemorrhages occur in the vicinity of the internal capsule, whereas in the child they are more apt to occur in or near the cortex. I had to fall back upon the theory that the greater delicacy of the superficial bloodvessels of the pia and of the cortex accounted for the more frequent cortical and meningeal hemorrhages in children. But I was also aware, thirty years ago, that intracerebral hemorrhages, embolism and thrombosis occur occasionally in children, exactly as they do in the adult, and that they give rise to clinical symptoms in no wise different from those of ordinary apoplexy. Much of this speculation was superfluous, since it is fairly well established at the present day that infantile encephalitis is much more common than it was supposed to be, and I have no doubt that some of the hemorrhages reported by former authors were part of an inflammatory process. In former years I could not accept Strümpell's well-known theory, that the acute hemiplegias of children were due to a polioencephalitis, which he thought akin to the poliomyelitic infection. Strümpell had no anatomic evidence to offer at that time, and his argument was based largely upon a few cases reported by Moebius and others, that cases of infantile spinal paralysis and infantile cerebral paralysis had occurred in several children of one and the same family. Strümpell's contention was no doubt extreme, but we have every reason to believe that he was correct in surmising the infectious encephalitic origin of many of these cases. Relying upon the resemblance to adult apoplexy, and in former years believing that adult apoplexy was invariably due to a vascular lesion, I depended largely upon a series of cases like one that I had occasion to observe in a boy, aged two and a half years, who after a simple attack of tonsillitis developed right hemiplegia with motor aphasia coming on without coma and without convulsions. The aphasia disappeared after two days and the hemiplegia also improved. Within a few weeks the young boy was entirely well

and scarcely retained a trace of the apoplectic condition. There was no history of syphilis in this case, and the entire development and retrogression of the symptoms reminded one of an adult apoplexy. I felt that the possibility of thrombosis could not be excluded, but whether hemorrhage or thrombosis, there could be no doubt that the lesion was intracerebral and not cortical, as in the majority of cases in children. Curiously enough, Déjerine, in 1891, reported 3 cases in which there were distinct hemorrhagic lesions in the vicinity of the larger ganglia, exactly where we nowadays find the chief sites of the encephalitic process.

Carrying the argument a little farther, let me state that in the recent epidemic of lethargic encephalitis we have had occasion to observe what appeared to be true apoplexies in the adult. The case of a well-known man in this city, whom I had the opportunity of observing in company with Dr. Dana, was particularly instructive. The patient presented for a number of days the typical clinical picture of a hemiplegia due, supposedly, to thrombosis. The development of partial paralytic symptoms on the opposite side of the body with dysarthria and some occular palsies proved, together with other signs, that in the adult acute hemiplegia may be the expression of an encephalitic process. There is less reason therefore than there formerly was to draw a sharp line of demarcation between the apoplexies of childhood and the apoplexies of adult life. Both in the adult and in the child we must now conclude that vascular lesions may be a frequent cause but not the sole cause, and in childhood I am now convinced that an encephalitic process of any of the well-known infectious types, lethargic, influenzal or what not, may be a frequent cause of these acute cerebral conditions.

I have not hitherto alluded to one question of great practical interest, and that is, whether or not convulsions *per se* produced paralysis in children or whether both the convulsions and the paralysis are due to the same cause. The truth, in all probability, lies midway between these extremes. In the distinctly infectious forms we may assume that the infectious process is responsible both for the paralysis and for the convulsions; but when a child has had a series of convulsions at shorter or longer intervals, and hemiplegia appears immediately following a severe convulsion, the venous stasis occurring during the acme of the convulsions may be held responsible for the development of the hemiplegia, and that this is not a mere theory but an anatomic fact has been definitely established by postmortem examinations of my own.

If we take up the points of difference and the points of resemblance between the palsies observed in children and in the adult we have still further reason to stress the possible and probable encephalitic origin of many of these cases. The startling difference noted in former years was the occurrence of choreic and

athetoid movements in association with the cerebral palsies of children, whereas in the adult such complicating disturbances of motility are relatively rare. Here again the studies of encephalitis have revealed the very striking fact that tremors, choreic, athetoid and myoclonic movements, are extremely common in association with the paralysis due to encephalitic conditions and the physiologic and anatomic studies of Hunt, Jakob, Vogt and many others have definitely shown that these unusual disturbances of motility, of posture and gait, are distinctly due to lesions of the extrapyramidal system.

Involvement of the neostriatum—the putamen—is held responsible for the development of double athetosis, a combination of choreic and athetoid movements. Lesion of the paleostriatum—the globus pallidus—is characterized by paralysis of automatic associated movements, by muscular rigidity and tremor: The clinical signs of paralysis agitans. When the entire striatal system is involved, as in Wilson's disease, we get a combination of rigidity and tremor with tonic and clonic spasms. It can easily be seen that the disturbance of motility associated with these early palsies may be ascribed to involvement of one or both striatal systems.

The corpus striatum stands in close relationship with the optic thalamus, and through it with the peripheral sensory apparatus, with the cortex cerebri and with the cerebellum.

I do not wish to enter into the many interesting details that have been developed in connection with the study of extrapyramidal diseases,* but must utter at least one word of caution, and that is, that it will not be safe to consider the globus pallidus or the putamen, or the striatal system as a whole, the sole site of the infantile cerebral palsies. The frequent association of idiocy, of imbecility, of epilepsy and the more frequent occurrence of convulsions in the cerebral palsies of children compel the conviction that the cortex must not be slighted or overlooked. Very careful examination of all parts of the brain will be needed to establish the complete pathologic record of these acute infantile cerebral palsies. If we accept the encephalitic origin for many of these acute spastic palsies we shall have no difficulty in explaining the occurrence of the unilateral as well as bilateral symptoms, and we need not be astonished every now and then to find diplegias as well as hemiplegias to be the expression of an acute or acquired cerebral lesion in childhood. Strümpell, who was right in so many things, was definitely wrong in maintaining that *hemiplegia* in children was synonymous with the acute infantile cerebral palsy. If his term, polioencephalitis, is to stand at all it must apply to the diplegic as well as to the hemiplegic forms.

* The subject has been discussed fully by Hunt, Jakob, Haberman and others.

Conclusion. In conclusion, let me emphasize the general proposition that, in attempting to classify or to interpret the cerebral palsies of children, the exact form of the paralysis is the unimportant factor. It is much more important to determine, whatever the form may be, whether the palsies are due to a morbid process that had its beginnings in the prenatal period or at the very time of birth, or whether they were acquired later in life as the expression of vascular accident, or as the result of an infectious encephalitis.

BIBLIOGRAPHY.

Batten, F. E.: On Cerebral Diplegia in Children, Clin. J., 1901, **18**, 33.
Batten with von Wyss: Brit. J. Child. Dis., 1915, **12**, 65.
Clark-Pierce: Am. J. Dis. Child., 1913, **5**, 425.
Collier, J.: Brain, 1924, **47**, 1.
Foerster: Deutsch. Arch. f. klin. Med., 1909, **98**, 216.
Freud, S.: Cerebrale Diplegien, Nothnagel's Spec. Path. u. Therap., 1897, **9**, 2.
Gowers: Manual of Nervous Diseases, 1893, **2**, 413.
Haberman, J. V.: The Amyostatic Syndrome, New York Med. J. and Med. Rec., 1922, **116**, 687.
Hunt, J. R.: Diataxia Cerebralis Infantilis, etc., Am. J. Med. Sci., 1918, **155**, 503.
Little: Trans. Obstet. Soc. London, 1862, **3**, 293.
McNutt, S.: Am. J. Med. Sci., 1885, **89**, 58; Arch. Pediat., 1885, **2**, 20.
Marie, P., and Fox: Rev. neurol., 1913, **25**, 346.
Osler: The Cerebral Palsies of Children, Philadelphia, 1889.
Peterson (Church and Peterson): Nervous and Mental Diseases, 9th ed., , 1924 p. 246.
Sachs, B.: Little's Disease, J. Nerv. and Ment. Dis., 1897, **24**, 723.
Sachs and Peterson: Jour. Nerv. and Ment. Dis., 1890, **15**, 295.
Spiller, W. G.: On Arrested Development and Little's Disease, J. Nerv. and Ment. Dis., 1898, **25**, 81.
Strümpell: Jahrb. f. Kinderheilk., 1884, **22**, 73.

INCIPIENT GENERAL PARALYSIS.

A Study of the Earliest Symptoms Presented by Seventy-four Cases.

By Henry A. Bunker, Jr., M.D.,

NEW YORK.

(From the New York Psychiatric Institute, Ward's Island, N. Y.)

The purpose of the study of which this paper is a brief report has been to determine as accurately as possible the nature of the earliest symptoms which made their appearance in a series of 74 male patients who were committed to the Manhattan State Hospital on account of fully-developed general paralysis during the past two years, and thereafter studied on the service of the New York Psychiatric Institute. The opportunity to investigate anamnestically the earliest departure from their normal state of health which

these patients manifested was enhanced by the fact that in a majority of instances cases were selected with the intelligence and observational ability of the informant (usually the wife of the patient) in mind. Thus, it is felt, has been obtained a fairly faithful picture of the patient at a stage in the evolution of his disease when he presented, at least from a symptomatic standpoint, nothing characteristic of general paralysis, as later seen and as commonly thought of, or indeed of neurosyphilis of whatever type; at a time when the patient, in other words, had advanced perhaps a single step beyond the strictly asymptomatic stage of the neurosyphilis which had been present in latent form, according to our present knowledge, almost from the time of his initial infection. If, then, the occurrence of certain symptoms can be shown to carry with it the possibility that, if not otherwise to be accounted for, they may have their origin in neurosyphilis and perhaps even in the more malignant form of that condition known as general paralysis, this fact will suggest the necessity for examination of the spinal fluid in numerous instances in which this procedure is not now carried out. For, obviously, the crucial factor in the diagnosis of neurosyphilis, and *a fortiori* of general paralysis, lies in the examination of the spinal fluid; and the essential practical problem involved consists in the recognition of the indications for such examination. Since the actual, if less immediate purpose of this study, is to indicate in a very partial way certain means whereby an earlier diagnosis of general paralysis may be achieved, we may take the liberty of preceding the discussion of our case material by a brief reference to the indications for spinal-fluid examination, without which a diagnosis of neurosyphilis is not seldom wellnigh impossible, and of general paralysis at an early stage of its evolution practically out of the question.

There are three phenomena, the occurrence of any one or more of which should raise the question of the desirability of lumbar puncture, while its omission in the presence of any two of these phenomena places the responsibility upon the physician who rejects the need for examination of the spinal fluid under these circumstances. These three findings are as follows:

1. A positive Wassermann reaction in the blood might not be considered as in itself an indication for lumbar puncture; yet it is the practice in the best clinics to perform a lumbar puncture upon every syphilitic prior to his discharge at the time the Wassermann reaction in the blood has been rendered negative. For every syphilitic is a possible neurosyphilitic; while it is also to be remembered that a not inconsiderable proportion of neurosyphilitics have a persistently negative Wassermann reaction in the blood serum. All "Wassermann-fast" patients are not neurosyphilitic; yet in many cases the persistence of a positive Wassermann in spite of protracted treatment is due to the presence of neurosyphilis. It is perhaps

of some interest, in suggesting, moreover, that these remarks are not wholly superfluous, that in an appreciable proportion of the patients in our series who early consulted a physician a positive Wassermann reaction was found to be present in the blood. Almost without exception, however, no effort was made, in spite of this fact and of the complaint of definite "nervous" symptoms as well, to establish the presence or absence of neurosyphilis. These same patients accordingly received antisyphilitic treatment of a purely routine character such as might conceivably have had a favorable influence upon neurosyphilis of the meningovascular and hence relatively "benign" type, but could not possibly be effective against the parenchymatous or "malignant" form of the disease from which these particular patients, as the event only too clearly proved, were beginning to suffer.

2. With or without a positive Wassermann in the blood, certain physical signs are, when present, distinctly suggestive, and sometimes practically proof positive, of the presence of neurosyphilis. Pupils which are unequal or irregular or which react to light with impaired briskness or degree of excursion are ground for strong suspicion, while in the true Argyll-Robertson pupil we have that medical *rara avis*, a pathognomonic sign—for a pupillary reaction of this latter type is practically pathognomonic of syphilitic involvement of the central nervous system. Absence or definite inequality of the knee jerks (or of the ankle jerks without absence of the knee jerks) is likewise a sign of highly suggestive value. On the other hand, the absence of any or all of these signs does not exclude the presence of neurosyphilis; nor is it possible, for obvious reasons, to state with exactitude what proportion of early neurosyphilitics do or do not exhibit them. When definitely present, they assuredly call for examination of the spinal fluid.

3. Certain symptoms, both physical and mental, of very varied character and in themselves relatively or absolutely undistinctive in their nature, occur with some prominence as the earliest manifestations of clinical neurosyphilis in many cases, and are at least equally characteristic of the earliest onset of general paralysis. In the presence of either of the two findings already mentioned, even the least distinctive of these symptoms may take on a significance which they could hardly otherwise possess. But with or without the coexistence of a positive Wassermann reaction in the blood or of suspicious neurologic signs, the occurrence of such symptoms, when they cannot be adequately accounted for on other grounds, should raise the question of their neurosyphilitic etiology and accordingly should make examination of the spinal fluid most desirable. Indeed, it may be laid down as a rule that the presence of any nervous or mental symptom whatever, if that symptom cannot be explained beyond reasonable doubt on some other basis, is cause for making an examination of the spinal fluid; such is the pro-

tean character of neurosyphilis and of its subspecies, general paralysis.

So far as our immediate topic, the early diagnosis of general paralysis, is concerned, the recent words of Stokes with regard to early tabes are equally in point: "The attention of the profession should therefore be focussed consistently on the subjective symptomatology, and when any of its leading points are developed in a case history, a quick search for early signs should be made as a routine," in order that, as he goes on to say, lightning pains shall no longer pass as "rheumatism" or "neuritis" in the face of absent pupillary light reflexes or knee jerks, "slow" bladders be called stricture, or gastric crises be operated on as gallbladder attacks. And while it is perhaps true that the analogous leading points in the diagnosis of early general paralysis tend from their mental rather than physical character to be more indefinite and more equivocal than is often the case in tabes, it is at least equally desirable that "nervousness" shall not demand simply a "rest cure" in the face of the physical signs just mentioned, nor a definite change in the patient's personality or emotional status be set down exclusively to worry or "nervous strain." This, then, is the justification for presenting, even though briefly, the results of our inquiry into the earliest symptoms of which 74 patients complained, who, nine months to even four years later, developed outspoken general paralysis, and in whom these early symptoms, whether or not accompanied by physical signs or a positive Wassermann in the blood, were in almost every case disregarded or misinterpreted. This error resulted, (1) because their possible significance was not appreciated, and (2) because their meaning was not further probed by a search for suspicious neurologic signs or confirmed by examination of the spinal fluid. Indeed, it might be claimed with some reasonableness that the early recognition of general paralysis has lately assumed an increased importance in view of the fact that we now have, in tryparsamide and in malaria, a therapy of such increased effectiveness that a striking degree of clinical remission with restoration of previous efficiency can be obtained in no small proportion of patients treated by these measures, provided only that they are treated early enough in the disease.

By far the commonest early symptom found in the patients in this series seems to be that which may be somewhat loosely termed *irritability*. It is usually stated that this manifestation is in sharp contrast to the patient's ordinary disposition, but there are, of course, instances in which the change represents an exaggeration, perhaps gradual but sooner or later definite, of a normal tendency to irritability on the patient's part. Or his emotional instability may take a somewhat different direction and manifest itself as a too ready, even if evanescent, emotional response of a sorrowful, depressive, or even tearful character. (It is perhaps interesting

that the opposite tendency to morbid elation or euphoria, which is often thought of as especially characteristic of general paralysis, does not once appear, at least in the present series, among the very earliest symptoms of the disease.) To these various manifestations of emotional instability, differing somewhat in kind and very distinctly in degree, the informant is prone to refer simply as "nervousness." This symptom was among the first to be noted in 42 of our 74 cases; in 18 it constituted the earliest departure from the normal observed by the informant; in 12 cases it followed some other symptom by a period of one to six months; in the remaining cases it was the third change noted in the patient, but in most of these its appearance was more or less simultaneous with that of the second. When this alteration in the personality of the patient was the first deviation from the normal to appear, it usually antedated the onset of frank mental symptoms by at least six months and not infrequently by a year, a year and a half, or even longer. In 1 case, indeed, a very intelligent informant was positive that a change in the patient of this description was observable nearly five years before the outbreak of acute psychotic symptoms. Irritability is, of course, far from being a distinctive manifestation. It is a characteristic of organic disease of the brain, is sometimes seen in diabetes and in nephritis, and may indeed be a reaction to any form of ill health. It is often a "functional" symptom and may form part of the clinical picture of a psychoneurosis. The fact that it occurs as one of the earliest changes in more than half of the present series of cases, however, suggests that its occurrence in a patient makes it desirable to exclude general paralysis as its possible cause.

Psychologically somewhat allied to this symptom, perhaps, is the condition referred to by the informants as restlessness. The patient is described as "nervous," "fidgety;" he is no longer content, as formerly, to remain at home after dinner, for example; he wants to be somewhere other than where he is, or to do something other than what he is doing. This is, perhaps, a more subtle alteration in the patient than even the milder degrees of irritability or of emotional instability, and it is possibly on this account that it appears in only six of our histories, and these among the most intelligent in the series. It is not unlikely that it accompanied or preceded the irritability in a number of the patients exhibiting the latter, and in fact the two symptoms are given as coexistent in the patient just referred to, in whom these antedated the outbreak of a definite psychosis by nearly five years. It is of interest, moreover, that the onset of this socalled restlessness preceded the appearance of frank mental symptoms by a considerable period; by a year or more in 2 of the cases, and by more than two years in the others.

The second most common of the earliest changes observed in this series might be considered the exact opposite of the preceding. It is

a symptom difficult to label with a single word, the term "quiet" being that which is most often spontaneously applied by the informant. The patient is described as gradually but noticeably becoming less active than is his ordinary habit; he becomes less communicative and may sometimes gradually lose almost all spontaneity of utterance; he often appears preoccupied, listless or apathetic; he wants to be let alone and is averse to the company of others, especially strangers, often leaving the room upon the advent of visitors; he loses interest in some of the things which formerly entertained him. It is a symptom that appears to correspond to some extent to that mental disturbance found as an occasional accompaniment of chronic epidemic encephalitis which has been termed by Naville as bradyphrenia and which in his description is characterized by "a diminution of voluntary attention, of spontaneous interest, of initiative, of the capacity for effort and for work." This change, in one guise or another, is described as among the earliest noted in 28 cases—the first alteration observed in the patient in 12 cases, and the second in 10. Although seeming on the face of it to represent a deterioration of a rather radical character, in these cases this symptom was usually first noted at least nine months before the onset of a frank psychosis, and in 2 cases was present for four and four and three-quarters years, respectively, prior to commitment.

Closely following in numerical importance this reduction of interest, this seclusive or "bradyphrenic" type of reaction, is *loss of weight.* Although there is evidence that a considerable proportion of these patients lost weight at some time during the evolution of their disease, only those cases are here included in which loss of weight was mentioned by the informant, nearly always spontaneously, as being an early and often rather striking manifestation. Of such cases there are 22 in this series. In 13 of these, loss of weight was the very earliest change noticed in the patient; in 9 it was preceded, often by a rather brief interval, by one other symptom; in no case was it preceded by two other symptoms. Indeed it is likely that some of the patients in this second group really belong in the first; for the onset of loss of weight is obviously difficult or impossible to date within weeks or even months, since it would usually not come to notice before it had amounted to at least 5 or 10 pounds, depending somewhat on the customary weight of the patient. The interval elapsing between the actual onset of loss of weight and the outbreak of frank mental symptoms is probably therefore in some cases an understatement; but it is noteworthy that this interval was never less than four to six months and was usually a year or longer, being at least two years in 1 case, more than three years in 3 cases, and nearly five years in 1 case. The amount of weight lost and the rapidity with which the loss took place and whether this marked the earlier or later period

of the evolution of the disease naturally varied widely in these patients. A loss of 10 or 15 pounds, often at the very outset, was almost invariable, since this would usually be nearly the smallest amount of loss discernible by the observer; a loss of some 25 pounds, took place within the first six months or so in several cases; and 3 patients lost a total of 35 pounds in weight, 2 of these within a year of onset. So far as this particular series is concerned, loss of weight appears, therefore, to assume some importance among the earliest symptoms of general paralysis because of its relative definiteness as a symptom, its early appearance and sometimes rather conspicuous character in an appreciable proportion of cases, and the fact that early and especially fairly well-marked loss of weight characterizes but few diseases—among which diabetes, hyperthyroidism and tuberculosis come most readily to mind.

Forgetfulness, a practically invariable characteristic of fully developed general paralysis, is mentioned as one of the earliest manifestations of the disease in only 15 cases, in but 5 of which it was believed by the informant to constitute the earliest abnormality present and in 7 the second to appear. In 1 case—and here the history was particularly detailed and complete—a mild degree of forgetfulness was noted by the patient's wife three years before the onset of acute mental symptoms. It seems probable, indeed, that this is a symptom which would for some time escape the notice even of intimates, although the patient himself might often be aware of its presence. Forgetfulness as a symptom has at all events the distinction, not shared by the three symptoms already mentioned, that its definite appearance de novo would make one think principally of either cerebral arteriosclerosis, on the one hand, or of cerebral syphilis or general paralysis, on the other.

Another symptom characteristic of organic brain disease, and occurring in this series as one of the earliest features of general paralysis in 15 cases, is an increased *tendency to sleep*. Even when relatively mild, such a tendency appears to come rather quickly to the attention of the patient's intimates. An analogy is seen in the pathologic sleep of many cases of epidemic encephalitis and in fact of other intracranial conditions such as brain tumor, and one is likewise reminded of the daytime dozing of the arteriosclerotic and the senile. In 8 of these 15 cases this symptom was the earliest to appear, according to the informants, but in 4 of these its appearance was considered to be essentially simultaneous with that of at least one other symptom; in 6 cases it was definitely the second abnormality in chronologic order. While the increased tendency to sleep made its appearance in most cases within but a few months before the outbreak of a frank psychosis, in 3 cases it was present for at least a year prior to that event.

The opposite manifestation—*insomnia*—was noted as an early phenomenon in only 9 cases, and in but 2 of these was it given as

the first symptom to appear, while in only 1 patient did it antedate the appearance of frank mental symptoms by any considerable period. In any event the wholly undistinctive character of insomnia as a symptom is self-evident.

Speech defect is, of course, characteristic of many cases of fully developed general paralysis, but it may also occur as one of the earliest symptoms. It occupies such a position in 11 cases in this series. It was the very first symptom noted in 5 patients, and in all of these it appeared some considerable time before the onset of definite psychotic symptoms—seven months in 1 case, a year or more in 3 cases, and five years and ten months in 1 case, while in a sixth patient it appeared, though not as the earliest symptom, a year and a half before the acute onset of his psychosis. In 2 patients the condition was of sudden onset. In several patients speech defect varied strikingly in intensity from time to time.

Defective judgment is a phenomenon also commonly associated with fully-developed general paralysis, being then usually so gross as to play a part in the most ordinary matters. But the question of early slight deviation from the individual's normal status in this respect is a subtle one, and such deviation may be as difficult of detection as judgment itself is difficult of measurement or definition. Few of our patients were in positions of responsibility such as to make lapses in this direction very apparent to the informant, or at least only after an interval of cumulative effect. Even when the informant can adduce evidence of this sort, it often remains something of a question whether the instance specified represents an early indication of the disease which subsequently develops or whether it is possibly something that might have occurred in any case and has only been made conspicuous by the later turn of medical events. For, obviously, it is by no means always possible to weigh the circumstances accurately enough to know whether a faulty investment or an ill-advised change in business, for example, was in fact an actual sign of the disease that was to develop a year or more later. At all events, there are but 7 patients in this series in whom judgment defect ranks as the earliest manifestation of mental disorder. In 3 of these the defect seems nevertheless to have been of the grosser order, an increasingly obvious mismanagement of their business which antedated other symptoms by a few months only. In 3 the situation was more difficult to estimate, the defective judgment manifesting itself four, six and nine months, respectively, before the appearance of any other symptom. In the seventh case it was learned from the patient himself, after he had achieved a very complete remission following malaria treatment, that nearly a year and a half prior to the onset of other symptoms, he had diverted funds of his in a way that to him was clear evidence, seen in retrospect, of mental disorder.

The remaining early symptoms are of a miscellaneous character,

represented each by a few patients only. Unusual *fatiguability* was early remarked in 7 patients; it was the first symptom to appear in 5 cases and the second in 1. In 1 patient it preceded any other symptom by six months, the appearance of frank mental symptoms by a year and one-quarter, and commitment by twenty-three months. Under this heading might be mentioned the early complaint of 2 or 3 patients of their awareness that there was something indefinable the matter with them, without their being able to say what it was—a feeling that they were somehow "not themselves." *Digestive disturbance* was the initial abnormality in 7 cases. In 1 of these it began three years before the actual mental breakdown and four years before commitment; in 2 cases it antedated mental symptoms by at least a year. In most instances the disturbance seems to have consisted of intermittent epigastric distress with little or no relation to meals; in 2 patients there was vomiting after nearly every meal, which passed off, however, in the course of three or four months. In 6 patients *impairment of vision* was mentioned as the very earliest evidence of disease. In 3 of these the condition rapidly advanced to optic atrophy and complete blindness, the onset of visual impairment antedating the appearance of definite mental symptoms by two, three, and six years, respectively. In a fourth case optic atrophy was unilateral. *Headache*, usually occipital, was prominent among early symptoms in only 4 cases; but it was the very first symptom to appear in only 1 patient. In 4 patients, *tremor*, usually of the hands, was noted among the earliest symptoms, but it was always preceded by at least one or two other symptoms. Three patients early manifested a *slowing in their movements;* it was in each case the second abnormality to appear, according to the informants, but followed the first at a brief interval of a month or two. A not uncommon manifestation of later general paralysis, it is perhaps the physical component of the bradyphrenic reaction which is frequently characteristic of even the earlier stages of the disease, while it also suggests the purely motor sluggishness seen in the Parkinsonism of chronic epidemic encephalitis. Of 4 patients it was stated that vague *rheumatoid pains*—in the shoulders, the arms, or the legs—appeared very early. In 3 cases they represented the very earliest symptom (appearing more or less simultaneously with digestive disturbance, however, in 2 of these), while in the fourth case this symptom, although the third to appear, did so nearly four years before the commitment of the patient was necessary. In 2 cases some unsteadiness of gait accompanied this symptom. In all 4 cases these pains disappeared after a few months. In 1 additional case it was stated that definite *numbness*, first of the right foot and presently of the right hand, made its appearance three and a half years before the onset of any mental symptoms whatever.

Fig. 1 presents in graphic form the relative incidence of these early symptoms in the 74 cases. It has been thought of some interest to distinguish between the frequency with which a given symptom appeared among the earliest abnormal manifestations, and the frequency with which it presented itself as the very earliest departure from the normal to occur.

Of the foregoing symptoms, which in this series have been the earliest to appear in cases of incipient general paralysis, it is clear that only three are in themselves at all suggestive of that disease, or of neurosyphilis of any type. These are speech defect, memory

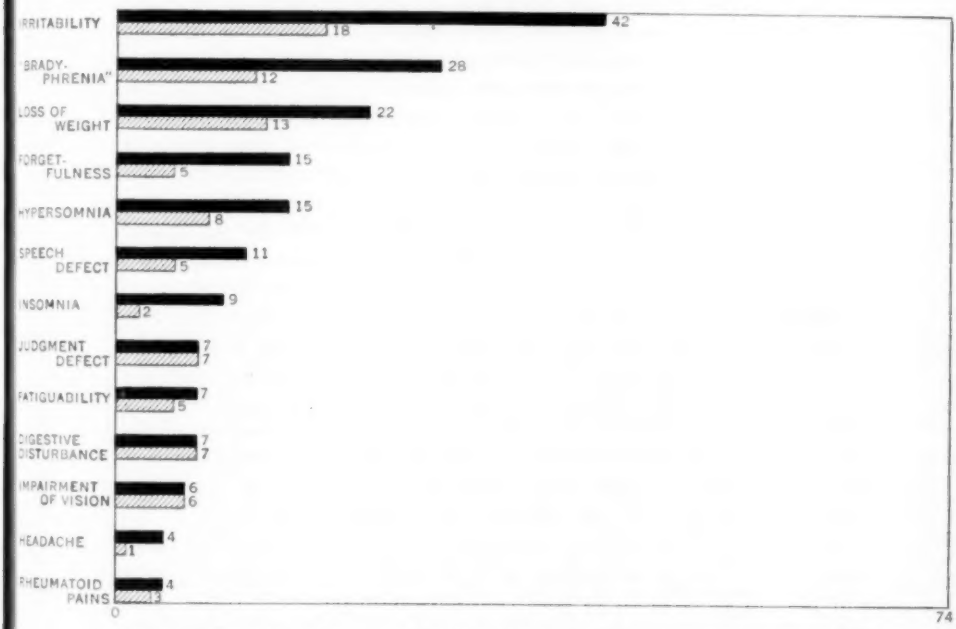

FIG. 1.—*Heavy lines:* Frequency with which a given symptom appears among the earliest changes noted. *Shaded lines:* Frequency with which a given symptom appears as the very earliest change noted.

defect, and judgment defect. The last named, though significant, is of reduced value because of the difficulty of establishing its presence; the existence of the first or second, although occurring as a relatively early symptom in only 15 per cent and 20 per cent, respectively, of this particular group of cases, should make examination of the spinal fluid imperative. Lacking in any such intrinsic diagnostic value but at least suggestive in view of its high numerical incidence as an early manifestation in more than half of the cases of this series, a history of irritability arising de novo should give sufficient ground for suspicion to demand the exclusion of general paralysis if the symptom cannot be accounted for with complete

certainty on a more obvious basis. Similarly, even though somewhat less common as an initial symptom, a history of personality change such as has been above described as an apathetic or seclusive type of reaction should be regarded in the same light. Loss of weight, although wholly undistinctive in itself, appears to be sufficiently characteristic of early general paralysis in many cases to suggest the possible presence of that disease in patients in whom other causes can be excluded. Finally, an increased tendency to sleep ranks almost with the first three symptoms just mentioned in both suggestiveness and incidence, and accordingly necessitates at least the keeping of the possibility of general paralysis in mind. The remaining symptoms—visual impairment, digestive disturbance, fatiguability, insomnia, headache, tremor, rheumatoid pains—have, of course, no diagnostic value whatever; all that can be said of them is that they occur in some incipient cases of general paralysis and that they are consistent with the presence of that disorder. But just as the possible relationship of even minor gastrointestinal symptoms to tabes has been repeatedly pointed out, so it is no less obvious that in the presence of this latter group of wholly ambiguous complaints it may become of only the greater importance at times to search elsewhere for their possible cause in neurosyphilis.

Summary. 1. If certain nervous or mental symptoms are consistent with incipient general paralysis, as certain ambiguous physical symptoms may be consistent with early tabes, then the presence of such symptoms in a patient, if they are not otherwise clearly to be accounted for, calls at least for examination of the pupils and of the knee and ankle jerks and for a Wassermann test, and raises the question, even when the evidence from these two sources is negative, of the necessity for lumbar puncture.

2. A study of the earliest symptoms which may occur in patients who later develop outspoken general paralysis, such as has been carried out in 74 male patients and here reported, may throw some light upon the symptomatic indications for the diagnostic procedures just mentioned.

3. In this study it was found that irritability holds first rank as an early symptom, since it occurred as the earliest abnormality, or one of the earliest, in 42, or 57 per cent, of the 74 cases.

4. The character change whereby an individual is reduced in activity and spontaneity, loses some of his interests, tends to withdraw into himself, and is often described as having become "quiet," is likewise a common early symptom, for it occurred in 28, or 38 per cent, of these cases.

5. Loss of weight as an early manifestation ranks third numerically. It occurred—and very often early—in 22, or 30 per cent, of this series.

6. An increased tendency to sleep, somewhat more suggestive in itself than any of the foregoing symptoms, was an early manifestation in 15 cases, or 20 per cent.

7. Speech defect, memory defect, and judgment defect have considerable diagnostic value in themselves, but they were found in this series among the earliest symptoms in only 11 cases, 15 cases, and 7 cases, respectively.

8. Visual impairment, digestive disturbance, insomnia, fatiguability, headaches, tremor, and rheumatoid pains were present as the earliest manifestations in a few cases; neurosyphilis must sometimes be considered in the differential diagnosis of these very undistinctive symptoms.

ALCOHOLIC INJECTIONS INTO NERVE TISSUES FOR THE RELIEF OF PAIN.*

By George I. Swetlow, M.D.,
NEW YORK CITY.

(From the Tuberculosis, Neurological and Surgical Divisions, Montefiore Hospital for Chronic Diseases.)

This is a report on a successful method of relieving pain applicable to a wide variety of conditions.

Ranson,[1] in his original researches on peripheral nerves, showed that a sensory peripheral nerve is made up of both medullated and nonmedullated fibers and that the nonmedullated fibers carry the pain-bearing influences (protopathic). Since these fibers are peripheral arms or projections of cells situated in the dorsal ganglia, it is quite evident that the destruction of these peripheral arms will interrupt the pathway of the afferent stimuli and thus prevent the influx of pain stimuli to the sphere of consciousness. The nonmedullated axones[2] take their origins from the small cells in the dorsal root ganglia while the medullated ones originate from the large cells.

The introduction of alcohol into a peripheral nerve produces an axonal degeneration involving mostly the small cells. The injection of 80 per cent alcohol[3] destroys not only the sensory components but also the motor components. The injection of a 60 per cent solution of alcohol, however, produces only slight transitory motor weakness, although the axonal degeneration of the afferent fibers and ganglia is quite extensive. The pathologic change[3] found in a sensory nerve and its ganglion cells following the injection of alcohol is the same as though the nerve itself had been cut, in other words, a Wallerian degeneration.

Pain in the following conditions will be discussed: (1) Laryngeal

* Read before the New York Neurologic Society, June 2, 1925, at the New York Academy of Medicine.

tuberculosis; (2) pleurisy; (3) several forms of headaches; (4) tabes with gastric crises; (5) cardiac disease; (6) pruritus ani.

Laryngeal Pain in Pulmonary Tuberculosis. The pain in laryngeal tuberculosis may be so severe as to interfere not only with rest which is vital to a tuberculous patient, but also with the ingestion of food because of the intense agony produced by swallowing. Any procedure, therefore, which offers relief for this frequent complication of pulmonary tuberculosis is a great boon to the sufferer.

In the search for relief many methods varying from mild applications to radical surgery have been tried with little success. Some of the methods briefly are: Orthoform or anesthesin insufflations, inhalation of chloretone vapors, insufflations of morphia, and submucous injections of novocain into the swollen tissues of the epiglottis and larynx. These methods have given very poor results. Operative interferences[4] (galvanocautery, curettage or amputation of the epiglottis[5]) have all ended disastrously, shortening life considerably. Another procedure[6] is to expose the superior laryngeal nerve surgically and either sever or crush it. Steinmann[7] reports 10 cases in which he resected the internal laryngeal branch with good results. Teller's[8] 12 patients obtained relief for a time, only to have the pain reappear.

In 1908, Hoffmann suggested injecting alcohol into the superior laryngeal nerve for the relief of these patients. He reported several cases with good results. His method was taken up by other workers but their reports as to success are conflicting. Lukens[9] reports 19 cases in which the shortest period of relief was three days and the longest period forty-one days after a single injection. I shall present 13 cases with the hope of encouraging the further use of this procedure and to controvert if possible a tendency to consider the method unsuccessful.

A clear conception of the anatomic course of the superior laryngeal nerve and the structures supplied by it is absolutely essential. The superior laryngeal nerve arises from the lower ganglion of the vagus, running downward and inward beneath both of the carotid arteries toward the superior horn of the thyroid cartilage About 1 cm. in front of, and a little below the cornu of the hyoid bone, the nerve divides into an internal and external branch. The internal branch enters the larynx by piercing the thyrohyoid membrane. It supplies the mucous membrane of the base of the tongue, epiglottis and the larynx. The external branch distributes its terminal filaments to the subglottic portion of the mucous membrane of the larynx and ventricle. It also gives off a few filaments to the pharyngeal plexus which supplies the constrictors of the pharynx. The ganglion of the trunk from which the superior laryngeal nerve arises, is in anatomic connection with the upper ganglion of the vagus which gives off an auricular branch. The auricular nerve courses along the inner surface of the facial

canal and terminates between the mastoid process and the external auditory meatus. The nerve supplies the skin of the posterior part of the auricle and the posterior inferior portion of the external auditory canal.

The technique for injecting the superior laryngeal nerve is as follows: The patient is placed in the dorsal recumbent position with a rolled sheet beneath the shoulders. This throws the head back and therefore moderately stretches the soft structures of the anterior aspect of the neck. The great cornu of the hyoid on the side to be injected is made more prominent by pressing with the left forefinger the great horn on the opposite side. A 5-cm. needle unattached to the syringe is inserted about 2 cm. median to and 1 cm. below the large horn of the hyoid. The needle is directed backward and slightly upward toward the great horn. The point of the needle must not be permitted to go laterally beyond a line joining the large cornu of the hyoid to that of the thyroid. Beyond this line the large bloodvessels of the neck are found. The point is pushed in for about 1½ cm. to lodge itself between the thyrohyoid muscle and the thyrohyoid membrane. One can be certain that the nerve has been struck only when the patient has a sharp pathognomonic pain in the ear on the homologous side which he indicates, not by talking, but by raising his hand. It is rare, indeed, to pierce the nerve directly. This occurred only twice in my series. After reaching the desired area the point is gently used as a probe to explore the entire thyrohyoid area and only after the characteristic signal is given is the syringe attached to the needle and the solution injected. The patient is cautioned against swallowing while the injection is in progress. The solution is a 60 per cent alcohol (warm) containing 1 per cent cocain hydrochlorid. The cocain is used to ameliorate the immediate local pain incident to the inflammatory action of the alcohol.

Before deciding to use the alcoholic form of treatment, a careful choice of the cases must be made. Those that have difficulty in swallowing due to other causes and not attributable to pain are to be excluded. The difficulty in swallowing under such conditions may be traced directly back to other parts such as the pharyngeal muscles which are supplied by the pharyngeal plexus formed predominantly by the vagus and glossopharyngeal nerves. One should investigate these nerves and elicit the cause for this motor deficiency. Only patients with spontaneous pain and those with painful deglutition are suitable for the injection of the superior laryngeal nerve.

The injection is done on the side which is subjectively most painful and here the patient can be of the greatest service. Often the more affected side is found by careful palpation eliciting greater sensitivity and tenderness.

One of the most frequent reasons for failure is that the alcohol

is not injected directly into the nerve. The thyrohyoid space is fairly large so that the 2 cc. of the alcohol injected spreads along the fascial plane, and little, if any, is absorbed by the nerve. The thyrohyoid area must be probed lightly and patiently until the nerve is encountered. Little pain is felt once the point of the needle has passed through the skin. The syringe must not be attached to the needle before the nerve is found. It is clumsy and heavy and as a result excludes fine probing. The possibility of pharyngeal tuberculosis as a cause of pain must be remembered. This condition may also explain some of the failures. Injections into the superior laryngeal nerve under such circumstances would not alleviate the pain.

Thirteen patients with advanced pulmonary tuberculosis and with specific laryngeal tuberculosis were treated.

(*a*) In one case there was complete failure to strike the nerve although several attempts were made.

(*b*) Eight patients who had intense pain and could swallow practically no food of any kind because of pain were completely relieved. One patient was free from all discomfort for twenty-two days. The pain recurred and after another injection she was again comfortable for an additional period of fifty-nine days to the date of death. Another was absolutely free from all discomfort for fifty-three days to the date of his death. Another is completely relieved for twenty-nine days to date. Another is almost completely relieved for twenty-three days to date, another for eighty days to date, another seventy-six days to date, another seventy-six days to date and still another, ninety-six days to date

(*c*) Four patients, though relieved of pain, have difficulty in "pushing the food down," as they put it. Various degrees of this difficulty are complained of. In fact, all of the cases treated had this motor disturbance which disappeared in a day or two. These few subjects still complain of this symptom. The apparent cause for this can be explained anatomically. The superior laryngeal nerve through its external branch contributes to the formation of the pharyngeal plexus, which latter supplies the constrictors of the pharynx. Complaints of the different patients vary in intensity. One was relieved of pain for fifty-two days to the date of his death, another thirty-two days to the date of his death, another nine days to date and still another eighteen days up to the date of his death. This last was an exceedingly severe case. In fact his epiglottis had been surgically removed in another hospital because of the intense pain.

(*d*) Immediate effects after the injections are: (1) Twelve patients complained of increased local pain lasting at most two days. (2) Nearly all patients complained of immediate motor difficulty in swallowing. Most of them clear up in a few days. (3) In only

two instances has there been a slight rise in the temperature curve the day after the injection.

Pleuritic Pain in Pulmonary Tuberculosis. The following is a presentation of five cases as a preliminary report of an apparently new application of alcoholic injections into nerve tissue for the control of severe thoracic pain caused by chronic pleuritic involvement. A careful search of the literature for any reference to this method has revealed no record of its previous use.

Although it is quite true that severe, agonizing thoracic pain is not common in pulmonary tuberculosis, nevertheless, there are cases in which the distress is so severe that it responds to no treatment. The method here described offers a means for the amelioration of this intense pain.

The upper six intercostal nerves[10] supply the upper parietal costal pleura. The lower six send their intercostal fibers to the lower parietal costal pleura as well as to the parietal pleura of the diaphragm. The center of the diaphragm is supplied by the phrenic nerve which is derived mainly from the fourth cervical nerve and also from the third and fifth cervical nerves of the cervical plexus. The phrenic nerve is not only motor to the diaphragmatic muscles, but also carries afferent sensory impulses from the parietal pleura to the cervical plexus. Disease in the costal parietal pleura will transfer its effects in the form of pain to the chest wall. The site of reference will depend upon the intercostal nerves impinged. Irritation of the parietal pleura over the central portion of the diaphragm will refer the pain to the neck which is the area supplied by the third, fourth and possibly fifth cervical nerves.

Since the intercostal nerve not only hugs the under margin of the rib but also is accompanied by the intercostal artery and vein, it was considered inadvisable to attempt to inject the nerve itself along the thoracic course. The more accessible structures, however, are the dorsal ganglia or dorsal root fibers entering the ganglia. The ganglia are found in the intervertebral spaces. The thoracic nerves immediately upon emerging from the intervertebral foramina lie midway between the transverse processes of the two adjacent vertebræ and run obliquely across the intercostal spaces toward the angles of the ribs above them to enter the subcostal grooves. As the nerves course from the intervertebral foramina to the angles of the ribs, they lie on the thin aponeuroses known as the internal intercostal fasciæ. These fasciæ extend to the tubercles of the ribs. The aponeuroses are the only layers separating the nerves in this location from the pleural cavity. This anatomic fact must be borne in mind during the injection.

Technique. The intercostal nerves that are to be injected, are those whose skin areas are hyperalgesic to pin prick. After having chosen the intercostal nerves to be injected the following procedure is executed. The patient is placed on the side opposite to the one

to be injected. The knees and hips are flexed on the abdomen and the head approximated to the lower extremities. This widens the intercostal spaces. Taking the twelth rib as a landmark the intercostal spaces to be injected are carefully palpated. A line running through the midline of the vertebral spinous processes is traced on the skin. At a point 4 cm. from this line and over the ribs which are above the spaces to be injected, wheals of 2 per cent novocain are raised. The wheals act both as a local anesthetic and as landmarks. An 8-cm. needle is inserted through each wheal. The needle is directed perpendicularly to the posterior surface of the rib just above the space to be injected. As soon as the needle impinges upon the rib, it is slightly withdrawn in order to change its direction, so that its shaft points 45 degrees downward, inward and forward toward the lower border of the rib. From the lower border of the rib, the point is advanced 2 cm. further. The point finds itself between the internal and external intercostal muscles. The same technique is used to approach the several hyperalgesic intercostal nerves. The needles are then attached to a water manometer to determine whether they are in the pleural cavity. Absence of extensive oscillations indicates that the needles are not in the pleural cavity. This precaution is taken to obviate the injection of alcohol into the pleural cavity. Three to 5 cc. of novocain are then introduced through each needle. After a few minutes the areas are tested for the presence of the previous levels of hyperalgesia. The disappearance or diminution of the hyperalgesia gives concrete evidence that the points of the needles are in the correct spots. Two to 3 cc. of 80 per cent alcohol (warm) are then injected through each needle. Half of the fluid is injected without moving the needle, while the rest is distributed with a little to-and-fro movement as the point is being withdrawn. The alcohol thus deposited produces an axonal degeneration of the thoracic nerve very near to its cell body in the dorsal ganglion. Some of the alcohol may even spread along to reach the intervertebral foramen and exert its action upon the ganglion itself.

The following is a brief résumé of the salient points presented by the cases treated: The pain may be sharp, sticking or tearing in nature, usually worse at night, preventing sleep. Lying on the affected side greatly increases the pain. Coughing or active movement greatly aggravates the distress. Pressure in the intercostal spaces produces pain. In the cases treated the duration of pain ranged from five weeks to five months. The patients were all suffering from far advanced pulmonary tuberculosis showing, either by physical examination or Roentgen ray evidence, the involvement of the pleura. Neurological examination showed in all these cases definite zones of hyperalgesia involving three to four intercostal nerves.

Following the injection there was usually an increase of pain for

a day or two especially at the site of injection, due probably to the local action of the alcohol. The zones of hyperalgesia usually gave way to hypalgesia. Pain on deep pressure in the intercostal spaces over the affected area became lessened or disappeared. The patients were relieved from their pain for the following duration: One case has been relieved sixty-three days to date, another thirty-six days to date, another seventy-one days to date, another one hundred and seven days to date, and another thirty-five days to date of death.

Headaches. Three cases of severe headache were treated. Two of them complained of occipital pain due to marked involvement of the great occipital nerve from cervical spondylitis; the third had severe frontal pains due to involvement of the right supraorbital nerve.

Each case showed an area of hyperalgesia over the involved nerve. Blocking these nerves with alcohol was followed by great relief extending from ten to twelve weeks to date.

Tabes with Gastric Crises. The search for a means to control the severe agony experienced in tabetic gastric crises has finally led to the application of surgery. The surgical treatment of gastric crises depends upon the hypothesis that irritative processes going on in the sensory sympathetic fibers of the stomach, after entering the coeliac plexus in the splanchnic major nerve finally reach the spinal cord through cells found in the dorsal root ganglia. The anatomic structure suggested the idea that if the posterior roots were severed, the painful stimuli would be interrupted in their course to the spinal cord. Following the suggestion of Moskowiez, Foerster[11] in 1911 practised posterior rhizotomy. This procedure was taken up by others. Although there were many brilliant results, the failures rose to 50 per cent according to Foerster and was accompanied by a mortality of 16 per cent Many of the patients experienced relief for as long as one and a half years. The cause of failure in so many of the cases according to Purves Stewart was that with severance of the posterior roots the central stumps remained and continued to convey painful stimuli. Sicard suggested that in order to obtain better results excision or avulsion of the root ganglia would be necessary. Sicard's conception is borne out by the results obtained in trifacial neuralgia; that is, excision of the Gasserian ganglion or cutting of the central fibers is the only way to give relief in intractable trifacial neuralgia. The operation itself is extensive, severing the root segments from the fifth to the eleventh dorsal segments on one or both sides. Others practised section of the spinothalamic tracts above the fourth dorsal segment However, with the introduction of alcohol paravertebrally the following advantages are noted: A rapid minor operation is done with little or no pain and with no danger to life, and the alcohol produces not only a degenerative effect on

the dorsal roots, but also seeps up to the dorsal ganglia, producing by chemical means what Sicard suggested should be done surgically.

The following case is that of a man suffering from severe tabetic gastric crises, referred from the neurologic service for treatment.

Patient C. R., male, aged fifty years, had had gastric crises for four years. For a period of nineteen days before this treatment was instituted he was in a constant state of agony, rolling wildly in bed. The agony was scarcely controlled by 3 to 4 gr. of morphia daily. Following the paravertebral injection of alcohol into the roots of the fourth, sixth and eight dorsal segments on the right side, and the third, fifth and seventh on the left side, complete cessation of pain ensued. For forty-nine days he has now been comfortable. The morphia has been reduced to a maximum of $\frac{1}{8}$ gr. one to two times daily.

Pain in Cardiac Disease. The question of cardiac pain has always been one of intense interest engaging the attention of the internist, the neurologist and recently that of the surgeon. In recent years many operations have been devised for its relief with varied results. No agreement as to which nerve to sever has been definitely reached. The treatment is empiric and unphysiological.

An interesting case report appearing in a French journal[12] in 1923 indicated a beginning of a method that supports our present procedure. The French case reported was that of a syphilitic patient, aged forty-one years, who was suffering from aortic insufficiency and angina pectoris. The pain was located retrosternally, on the anterior surface of the left half of the chest and down the arm to the elbow. Eight centigrams of procain were injected into the second and third dorsal spinal roots. Sensory examination indicated that these levels be injected. One half hour later the patient was put through numerous tests and although the pulse rate rose from 80 to 140 beats per minute and he suffered from great shortness of breath and palpitation, there was no pain. The same efforts were repeated at the end of six hours when the effects of the procain had partially passed off. Although the characteristic pain reappeared, it was much milder. It was then decided to sever these irritable roots, but the operators were forced to stop after the second dorsal root was cut because the patient collapsed. These writers feel that the principal afferent sensory impulses pass from the heart and aorta through the ganglia and roots of the eighth cervical, and of the first, second, third and fourth dorsal nerves. The report of this case with the case to be reported by us strongly suggest the idea that pain impulses do pass to a great extent through the dorsal roots. More cases will be necessary to place this conception on a firmer basis.

The following patient was referred from the service of Dr. B. S.

Oppenheimer. It is the first case on record that has received paravertebral injection of alcohol for the relief of cardiac pain.

Patient R. C., female, aged twenty years, is suffering from aortitis and aortic insufficiency caused by congenital syphilis. Her complaints of pain began April, 1923, with pain over the precordium. In a few months the discomfort extended to the left shoulder blade and the back of the chest on the left side. The pain was sticking and constricting in character and especially worse during the night. Since April 17, 1924, the pain has been more severe. The attacks consist of paroxysms of severe sticking pain lasting a few minutes and leave in their wake a dull ache over the same area. These paroxysms are brought on with only slight exercise and as a result greatly curtailed physical activities. A zone of hyperalgesia was found extending from the fourth to the seventh dorsal segments on the left side. The following was the treatment that she was given during her stay at the hospital: (1) A course of arsphenamin and mercury salicylate which was completed October 2, 1924; (2) potassium iodid which was discontinued several months ago; (3) a series of injections with Bismogenol. Following this series of treatments she was more comfortable.

After the paravertebral injection of the fourth, fifth, sixth and seventh dorsal roots on the left side she was greatly relieved. The relief consists in her ability to carry out greatly increased physical activities with diminution in the number and severity of the attacks of pain. Before the injection of alcohol she was unable to walk more than one block because the pain was so severe that she was forced to stop. The distress lasted two to three minutes. Now she can walk from five to ten blocks and although she at times develops pain she asserts that it is so mild and fleeting that little attention is paid to it. Previous to the alcoholic injection she found that on attempting to practice on the piano more than ten to fifteen minutes, she would be forced to stop because of the agonizing pain. Now she plays at least one hour and at times longer with only an occasional pain. For the past forty-one days she has had relief.

Pruritus Ani. The lack of success which the dermatologist and proctologist have had in the treatment of pruritus ani is well substantiated in the literature. Itching is a stimulus of afferent impulses whose intensity is below that necessary to call forth a perception of pain. The general conception is that the condition is due to an involvement of the cutaneous nerve endings. This disturbance causes itching and the resulting scratching induces fibrosis in the dermis, fissures, ulcerations, and thickening of the tissue about the anal opening. Many of the cases are cured by removing the local disturbance. However, patients who have been

suffering for more than two years are often not relieved even if the local lesion is removed. Frequently in these troublesome cases a severe pruritus is present and no local lesion is seen. Treatment in these advanced cases with Roentgen ray and excision of the cutaneous nerves to the skin in the anal region have been partially successful. The case to be reported was treated by the introduction into the epidural space of a 20 per cent solution of alcohol in saline solution. The results obtained were so striking that the report of this case is of apparent value. The literature shows no reference to this application.

Patient J. W., male, aged sixty-one years, is suffering from a vascular lesion which produced a right hemiparesis. The itching about the anus began three years before his admission to the hospital. It was especially troublesome during the night. He was forced to rise and attempt to obtain relief with vigorous rubbing with a towel. Immediately after having a bowel movement this itch would become especially severe and persist from a half to one and a half hours. He was admitted to the neurologic wards at Montefiore Hospital one and a half years ago. From the date of his admission his complaints concerning the itching were constant and pitiable. His sleep during the night was greatly disturbed. He was seen by the dermatologist and prescribed for without avail. Following our suggestion an epidural injection of 80 cc. of saline and novocain was made with no relief at all. On May 12, 1925, eighteen days ago, a solution of 20 per cent alcohol in saline to make a total quantity of 75 cc. was introduced into the epidural space. He was immediately relieved. That was eighteen days ago and he is still comfortable. This method might be of special value in those cases in which the itching induces scratching and as a result inhibits the local healing power. The controlling of the itch together with the local treatment should be of great aid in helping these patients.

Summary. I have attempted to present a series of cases, diverse in nature, in which alcoholic injections into the nerves were made, in order to obtain relief from excruciating pain.

The cases in which thoracic and cardiac pain was relieved are presented merely as a preliminary report.

The alcoholic injections into nerve tissues for the relief of pain have been in our hands a valuable therapeutic procedure.

BIBLIOGRAPHY.

1. Ranson, S. W.: Anatomy of the Nervous System, 2d ed., p. 67.
2. Ranson, S. W.: Ibid. p. 63.
3. Byrne, J.: J. Nerv. and Ment. Dis., 1921, **53**, 433.
4. Fishberg, M.: Personal communication.
5. Boldt, R.: Dissertation, Rostock, 1906, p. 41.

6. Bjalo, D.: Die Tuberkulose (Moskau), 1922.
7. Steinmann: Verhandl. d. 15 Kongr. Russischer Chirurgen, Petrograd, 1922, **9**, 25.
8. Teller, W.: Ztschr. f. Tuberc., 1922, **36**, 35, 36.
9. Lukens, R.: New York Med. J., 1918, **107**, 353.
10. Pottenger, F. M.: Symptoms of Visceral Disease, 1919.
11. Foerster: Proc. Roy. Soc. Med. (Surg. Sect.), 1911, vol. **4**.
12. Danielopolu, D., and Hoistide: Bull. et mém. Soc. méd. de hôp. de Paris, 1923, **47**, 69.

FUNCTION OF THE AUTOGENOUS KIDNEY TRANSPLANT.

By Kenji Ibuka, M.D.,
special student, the mayo foundation, rochester, minn.

(From the Division of Experimental Surgery and Pathology, Mayo Foundation.)

Since the development of a successful method of bloodvessel suture has made transplantation of whole organs possible, many experimental studies have been made on the transplantation of the kidney. The possibility of transplanting organs by vascular anastomosis has not only been proved, but a reliable surgical technique for the purpose has been established. This method has opened a new and broad field for experimental studies on the kidney with an approach to some very interesting problems. Many are mainly of interest from the physiologic standpoint, others chiefly of surgical interest. One suggestion of practical significance was the long-cherished surgical dream of possibly substituting a healthy organ for a diseased one. The perfection of a method of bloodvessel anastomosis and improvements in surgical technique seemed to offer a rapid realization of this dream. In regard to the kidney it was readily shown that autotransplantation of the organ could be successfully accomplished, and in a high percentage of instances a good functional result secured. However, for it to have any practical value it is necessary to employ homogenous or heterogenous transplants, and the results of such transplantation showed that there were seemingly other factors involved than those encountered with the autogenous transplant.

This investigation was undertaken to advance further experimental explanation of this difference between the autogenous and the homogenous transplant and to investigate the functions of the autogenous kidney transplant in detail, by comparing them with those of the other normal kidney, by observing the function of the transplant before and after removal of the untouched sister organ and by observing at the same time the general condition of the animal. Also it was hoped to establish a definite standard of function of the autogenous transplanted kidney for comparison with the function of the homogenous transplanted kidney, as presented in the succeeding paper.

Review of Previous Work. As more than thirty studies on autotransplantation of the kidney have been published, it is only possible to present their general results. Various sites have been employed for the attachment of the transplant, including the neck, inguinal region and various points within the abdomen. In accordance with the site chosen, either the common carotid artery and jugular vein in the neck, femoral vessels in the inguinal region, or the iliac, splenic or the renal vessels in the abdomen were used for anastomosis to the renal artery and vein of the transplant. In some investigations the organ has been left *in situ* and the renal vessels severed and anastomosed, or both the aorta and vena cava have been severed above and below the entrance of the renal vessels and anastomosed. The simple end-to-end method of suturing vessels has been most often used and considered the best. For the management of the ureter of the transplant, in order to drain the urine properly or to serve the purpose of observation, the ureteral end was sutured directly to the skin, the wall of the esophagus or the wall of the bladder. The first investigators contented themselves with demonstrating the possibility of transplanting the kidney, establishing the proper surgical technique, observing the excretion of urine from the transplant in its new situation and maintaining the life of the animal by the transplanted kidney alone. However, with the elaboration of a successful surgical technique for transplantation of the kidney, histologic and functional studies become the center of interest, because no crucial evaluation of the results can be obtained otherwise. The latter investigations have scarcely done more than show the magnitude of the problem. The recent development of modern methods of analyzing chemically, particularly by micromethods, the principal constituents of urine and blood, together with the advent of reliable methods for testing the functional efficiency of the kidney, have made a more detailed study of the effect of transplantation of this organ of great interest and possibly of practical value.

Operative Technic and Method of Observation. All experiments were performed on active, well-nourished mongrels, weighing about 10 kg. Animals of good disposition were chosen to insure ease in handling them, and short-haired dogs were selected so as to minimize the danger of infection of the wound by hair. Whenever possible, female animals were chosen, as urine could be obtained from the bladder without difficulty. The neck of the animal was used as the site for transplantation, as the excretion from the transplant could be readily observed, and the urine could be collected without soiling, and separately from that of the other kidney. Thus the function of both kidneys could be compared, and the change of function of the autotransplant before and after the removal of the untouched kidney could be accurately followed (Fig. 1).

The operations were carried out under ether anesthesia, with the strict aseptic technique which is necessary to insure success in the experiment. The bloodvessels of the neck were first prepared, and then the left kidney, after being excised through an incision in the median line, was carefully wrapped in a warm salt pack and transferred to the neck for future engrafting. The renal artery was anastomosed to the common carotid, and the renal vein to the external jugular vein, the usual end-to-end method of suturing bloodvessels being employed, as described by Carrel and Guthrie. The ureter was brought to the outside through a small separate

FIG. 1.—(Dog H-745). Photograph showing method of collection of urine specimens from the transplanted kidneys in the neck. The right kidney (above) was transplanted four days before, and the left kidney (below) fifty-one days before this picture was taken.

stab wound in the skin, and the kidney placed in a muscle pocket in the region of the carotid sheath, after the reëstablishment of circulation through the organ was assured. These procedures were always followed with painstaking care, in order to avoid hemorrhage, traumatization of bloodvessels or other harmful effects on the transplant. Further details of the technic are not given, since it has been described by Guthrie, Williamson and others.[5]

As a routine the wounds of the neck and the abdomen were closed without drainage. Collodion gauze dressing was used on all except the stab wound through which the ureter passed. A small sterilized ureteral catheter, the tip of which had been smeared with

vaselin, was inserted into the ureter to the pelvis of the transplant. The distal end of the ureter was tied around with No. 00 catgut to hold the catheter in position and control the bleeding from the ureteral bloodvessels. This ureteral stump was allowed to protrude from the stab wound to a length of from 1.5 to 2 cm. It was not sutured to the skin because the neck and the ureter were usually swollen more or less for two or three days after the operation, and also because the movement of the neck immediately after the transplantation might cause some slight dislocation. If the ureteral stump were fastened to the skin the ureter might sometimes be drawn too tight or be kinked, and thus obstruct the blood supply to the kidney or prevent the free drainage of excreted urine. The protruding part of the ureter was pasted with sterilized vaselin and covered with a small gauze sponge for protection until the animal recovered from the anesthesia, soon after which it was removed. For several days following the operation the ureter and the surrounding part of the skin were frequently treated with a wet dressing of Dakin's solution, as they were quite often contaminated superficially by soiling, especially with urine.

The catheter was usually left in position from forty-eight to seventy-two hours after the operation, because drainage of the excreted urine was frequently hindered by swelling, both of the ureter itself and of the surrounding tissues. However, by the time the adhesion and adaptation of the ureter to the surrounding tissues was established the further drainage of urine to the outside readily took place without the catheter. In spite of all precautions, a small amount of blood dripping over the end of the catheter sometimes clotted at the opening, or mucus excreted from the pelvis plugged the lumen of the catheter. When this occurred the catheter was washed with sterilized salt solution or distilled water, or was changed. The catheter could often be kept patulous by giving an abundant supply of water or milk to the animal and thus encouraging diuresis.

At the operation the excised kidney looked pale yellowish and flabby before reëstablishment of circulation through it; but when the anastomosis of bloodvessels was completed the kidney soon assumed a normal reddish color and normal consistency, and showed apparent pulsation of the artery and engorgement of the vein. It should be mentioned that marked tenseness of the kidney was evident immediately after the reëstablishment of the circulation, but after one or two minutes it rapidly passed away. By the time the wound was closed frequently small amounts of urine were being discharged from the catheter in the ureter.

During the experiment, after transplantation had been performed, the diet was regulated, specimens of blood and urine were taken at various times for chemical analysis and observations on the excretion of the transplant frequently made. As good-natured dogs

were chosen for the experiments, gentle handling and loose tying of the animal on the observation table, which had been especially constructed for this work, soon accustomed the animal to lie quietly and with ease for long periods. Observation was thus facilitated, and chances of disturbance of the transplant or interference with the results of the experiments were minimized. Thus, the collection of urine from the transplant into the test tube through a clean, short ureteral catheter, the catheterization of the bladder on every necessary occasion, and the injection of dye or drugs were carried out without difficulty (Fig. 1).

The time taken for the transplantation was usually about an hour and thirty minutes, but the time during which the renal circulation was interrupted was between twenty and thirty minutes, reckoned as the time which elapsed between the clamping of the renal bloodvessels and the reëstablishment of the circulation through the carotid artery and jugular vein. As the experiments of autotransplantation of the kidney were used to develop technique for the second phase of the problem, that of homotransplantation, my percentage of successes was not as high as if the series had been started after the requisite technique and skill had been acquired. For this reason the number of experiments and percentage of successes are not given. While many of the experiments were partially successful, detailed studies have been made on eight autotransplanted kidneys.

The following tests were made:

CHEMICAL ANALYSIS OF BLOOD AND URINE.

Blood.	Urine.
Nonprotein nitrogen (Folin and Wu)	Total nitrogen (Folin and Denis)
Urea nitrogen (Folin)	Urea nitrogen (Van Slyke and Cullen)
Creatinin (Folin)	Ammonia nitrogen (Folin and Farmer)
Chlorid (Whitehorn)	Chlorid (Whitehorn)
	Sugar (Benedict)
	Reaction (Litmus paper)
	Phenolsulphonephthalein (Maclean, using Kober's colorimeter)

Results of Experiment. In common with most investigators, I occasionally encountered thrombosis of anastomosed bloodvessels, infection of the wound, as well as of the transplant itself, displacement of the kidney in the new location, kinking of the ureter and retraction of the protruding ureteral stump from the stab wound. Those are the main troubles which lead to failure of the experiments immediately after transplantation. With mastery of the surgical technique, however, and the carrying out of proper care for the treatment of wounds and of the animals themselves, it was possible to maintain a kidney transplant successfully, even in the neck of the dog, with results much the same as those of Dederer and Williamson. Although in the neck the persistence of the kidney may not be per-

manent, still the duration (over ten months) of its function is quite sufficient for the investigation of many problems concerning transplantation and functional activity of the kidney.

The circulation of the kidney is interrupted for a certain period (at the most, thirty-five minutes), but the organ can stand, and apparently recover from, such effects if accurate technique and proper care are instituted. Such a well-transplanted kidney in the neck of the animal carries out its normal functions thereafter for months, while the other kidney functions in the abdomen. Even after excision of the other kidney, whether within a few days or after a fairly long time (over six months), the transplanted kidney is able alone to maintain the normal life of the animal for a long period (four months). The transplant responds, therefore, to the excessive demand set up by experimental procedures, as well as to physiologic processes. This fact shows that, although the kidney is a very delicate parenchymatous organ and sensitive to interruption of its circulation, as proved by certain investigators, still it has a power of resistance and an ability to recover if the interruption is limited to a certain period of time.

Urine from the transplants, obtained both before and after the removal of the unmolested kidney, is fairly normal so far as its concentration and main constituents are concerned. Albumin in the urine from the transplant is found in most cases immediately following transplantation; it soon disappears, however, if transplantation and the postoperative course are uneventful. Urine from the transplant is alkaline during the immediate period after transplantation, but later it is often acid. Concentration of chlorid is usually much higher than that in urine from the untouched kidney during the first period after the operation, but later this difference is not so marked. Those changes of reaction and of concentration of chlorid resemble the results from the urine of denervated kidneys. On the other hand, excretion of nitrogenous substances, of phenolsulphonephthalein, as well as of sugar after injection of phlorhizin, is in most cases less in the urine from the transplant than in the urine from the sister organ in the abdomen, both immediately after transplantation and later.

The transplant excretes phenolsulphonephthalein, in a small percentage and with slight delay of onset, immediately after the transplantation. Parallel with recovery from the immediate effects of the operation, however, elimination of the dye increases, not only in quantity but also in promptness, on the average two minutes after its intravenous injection.

After the excision of the remaining kidney an apparent increase in the rate of excretion from the transplant is manifested, not only by the volume of urine excreted in a certain period of time, but also by the excretion of phenolsulphonephthalein. The absolute amounts of the dye vary in each case, according to the condition of

the transplant. It was often discovered on operating that the kidney to be used for the transplant showed some pathologic condition, such as scarring due to infection or advanced age of the animal. However, if the organ is normal, and has been successfully transplanted, the elimination of the phenolsulphonephthalein soon reaches the normal limit of excretion through both kidneys, although the absolute amount of excretion during the first hour after the injection (the highest output, 55 per cent) always remains slightly diminished compared to the amount excreted by both kidneys after transplantation. But concentration and onset of excretion of phenolsulphonephthalein show no marked change until hydronephrosis and infection have caused dysfunction of the transplant. At this time both decrease of excretion and delay in appearance are noted.

Furthermore, the equilibrium of nitrogenous constituents, as well as the amount of chlorid and sugar in the blood, shows no remarkable change before and after transplantation, or even after excision of the remaining kidney. It can be concluded that the excretory function of the transplanted kidney alone is sufficient to keep them normal as long as the transplant is in full activity. Near the end of life, in such animals as suffer from disease of the transplanted kidney, those nitrogenous constituents of the blood accumulate until the animal finally dies with the typical symptoms of uremia. Excretion and character of urine change at this time also, for albumin casts and pus cells appear and increase, while the amount of urine decreases.

The regulatory activity and the response of the transplanted kidney to the demand set up by experimental procedures, such as the injection of phlorhizin, the administration of such pharmacologic substances as sodium salicylate, the increased intake of water or physiologic solution of sodium chlorid or glucose by mouth or by intravenous injection, are fairly normal when the transplant is in good condition. The diuresis caused by water or physiologic salt solution, which is administered through the mouth and absorbed from the alimentary tract, leads to an increase of urine which begins in from twenty to thirty minutes after these substances are swallowed, reaches its maximum at one or two hours and then falls slowly to normal.

These results coincide with the observations on diuresis made by other investigators in the excretory process of normal kidneys. Also the relation of excretion of total nitrogen and chlorid in the urine during such diuresis is nearly the same as that experimentally observed in the normal kidney. When water is given by mouth in large quantity the percentage of nitrogenous constituents falls, whereas when physiologic salt solution is given in the same way neither the nitrogenous constituents nor water is much affected, although the percentage of chlorid relatively rises.

Peristalsis of the ureter is observed during the operation, even after the kidney is removed and before the circulation through the organ is yet reëstablished. However, after reëstablishment of the circulation it shows more activity than during the interruption of blood supply. The periodic flow of urine from the distal opening of the ureter of the transplant, and even the expulsion of the inserted catheter, are also observed, beginning several days after transplantation, and this periodic flow of urine increases to such a marked degree at last that the ureter really squirts urine in a thin stream about a half foot from the animal, at frequent intervals. This is especially noticeable near the end of the animal's life, a fact which coincides with the observations of Dederer and Williamson.

The well-functioning kidney transplants have a practically normal anatomic appearance of the vascular and tubular elements, although some scarring may be found in a few areas (Figs. 2 to 5). On the other hand, those of the disabled transplant show hydronephrosis and infection. The hydronephrosis usually does not proceed to the extreme extent of destroying parenchyma mechanically, but rather infection of the renal tissue in the form of pyelonephritis prevails, as manifested by cellular infiltration, proliferation of connective tissue and destruction of the essential elements of renal tissue. However, the glomerular tufts are relatively well preserved, even while the cellular elements of the tubules fall into marked atrophy, degeneration and even necrosis.

Discussion. The proper choice of the site for transplantation of the kidney is a most important factor in the success of the operation, as well as in the restitution of the function of the organ. However, if reimplantation in the natural site alone is favorable for the maintenance and the persistence of good function of the kidney, as some investigators concluded, the procedure is robbed to a large extent of its experimental value as well as its clinical application. The feasibility of transplantation of the kidney as an actual operation should be so firmly established as to make it applicable even in the presence of certain differences of blood pressure and blood supply, lack of original protection by surrounding organs and exposure to certain mechanical insults and to the infection which must be expected in the cervical region. Success with transplantation of the kidney in the neck of the dog may establish the feasibility and value of the operation not only for experimental, but also for clinical, purposes, although the latter may be only rarely carried out.

It is also desirable to determine whether function of the transplant continues in the new location, coëxistently with the normal kidney in the abdomen or not, and if it does it would possibly be of clinical value to know how long it is normally maintained. Some investigators have inclined to the view that the transplant does not coöperate with its sister organ, and that it loses its activity

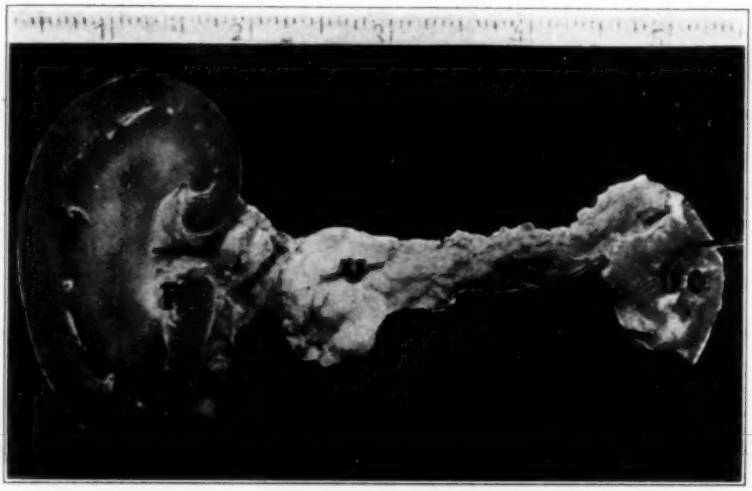

FIG. 2.—(Dog. H-351). The gross specimen of a successfully transplanted kidney that had functioned normally for ten months; the animal was killed at the end of this time. Normal appearance of the cut surface of the kidney, slightly dilated pelvis (P), perfectly patent ureter (U), and ureteral opening in the skin (U.O.).

FIG. 3.—(Dog. H-351). Photograph of kidney and vessels showing good healing of the anastomosed bloodvessels of the transplanted kidney. The sutured parts (dark mark indicated by double headed arrow) of artery *A* and vein *V* show smooth luminal surfaces, slight thickening of perivascular connective tissue, but no stenosis.

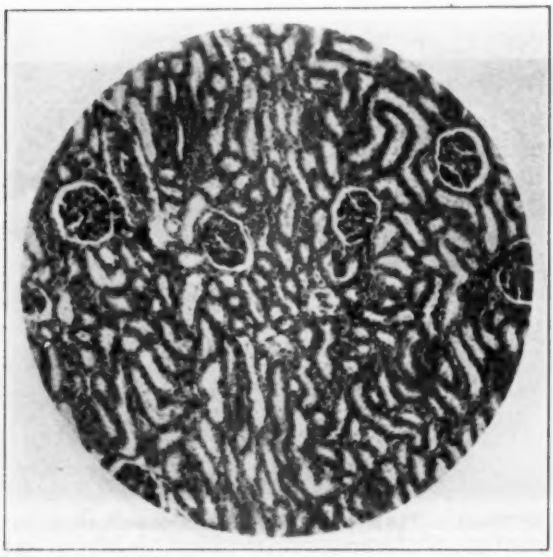

FIG. 4.—(Dog H-351). Photomicrograph of section from the transplanted (left) kidney that functioned normally in the neck for more than six months (coëxisting with the right kidney in the abdomen), and after the removal of the latter, 121 days alone. Apparent hypertrophy of glomerular tufts as well as tubular cells, but structure normal. (Compare with Fig. 5.) (× 60.)

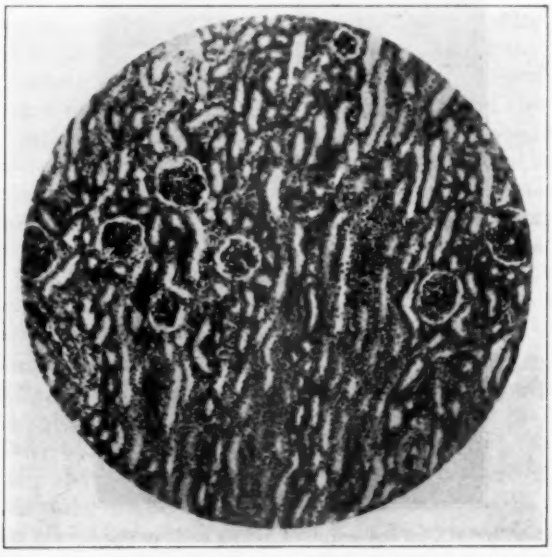

FIG. 5.—(Dog H-351). Photomicrograph of section from the right kidney which was removed from the abdomen 189 days after the left kidney had been transplanted. Renal tissue is normal. (× 60.)

of function by atrophy, owing to a decrease or a lack of normal functional stimulus, unless the other kidney is removed shortly after the transplantation. In one of our experiments the remaining normal kidney was removed from one dog one hundred and eighty-nine days after the transplantation, and the animal was surviving in good health four months later.

The existence and extent of the reserve functional power of the kidney have often been discussed, their proof being as important a question in the kidney as it is in the heart. The present experiments have not answered the question whether this compensation is borne by the functional reserve power of the kidney alone, or whether by the help of other organs. The results of urinalysis and functional tests show, however, that the transplanted kidney soon responds to the physiologic demands and even to the excessive call occasioned by experimental procedures after ablation of the other kidney.

The literature on the influence of the renal nerve on secretion is voluminous, and many workers have studied the efficiency of the denervated kidney. The conclusions of these investigators can be arranged in two classes: The first assumes the existence of secretory fibers in the extrinsic nerve; the second denies it. The most reliable method of excluding the influence of the nervous system through the extrinsic nerve of the kidney may be the transplantation of the kidney in a different site, since the possibility of regeneration of nerve is not entirely excluded in the case of reimplantation. My results lead to the conclusion that the extrinsic nerve supply plays a minor and not an essential part in renal function.

Many factors, such as changes in the circulation or the mechanical condition of the outflow of the urine, or the direct pressure on the kidney itself, as well as denervation, affect both the quantity and quality of the urine excreted by the transplanted kidney. The results of the experimental and clinical observations do not coincide in all details. In the transplantation of the kidney some change of local blood pressure or blood supply to the transplant is likely to occur, as the range of blood pressure between renal artery and vein is different from the range between the carotid artery and jugular vein. Also alteration of the normal outflow of urine from the kidney may be occasioned by the insertion of a catheter into the ureter immediately after the operation and later by the obstruction of free drainage that is caused by the contraction of the muscles of the neck and the cicatricial constriction of the skin around the ureteral opening. The possibility of difference of the direct pressure on the kidney by the surrounding tissues should also be considered, as the kidney is removed from the abdomen and put into the muscle pocket in the region of the carotid sheath. Furthermore, the metabolic, circulatory and other pro-

cesses of the living organism, which go to make up the general condition of the animal, may have an influence on the renal function and change the quantity and the quality of the urine from the transplant. However, it was observed that the transplants excreted urine which was always nearly normal in physical properties and chemical constitution. Therefore, it can be concluded that, in spite of adverse influences, the transplanted kidney shows as much power of adjustment as the normal kidney.

The innervation of the muscles of the renal pelvis and the ureter by the extrinsic nerve has been discussed by many investigators from the anatomic and physiologic standpoints, and, since the question has not yet been decided, the paralysis of the ureteral muscles, occasioned by the loss of innervation through the extrinsic nerve supply, is accounted a cause of hydronephrosis by some clinicians and investigators. In some of my transplants hydronephrosis was observed, but at the same time marked activity of peristalsis of the ureter was noted which increased enough to eject urine in a fairly long stream at frequent intervals. This hydronephrosis in the transplants may be attributed mostly to mechanical factors, such as the obstruction of free drainage by the contraction of the muscles of the neck as the animal moves its head from side to side, or by the cicatricial constriction of the skin around the ureter, with probably actual atresia of the ureter. The atresia of the ureter did not appear to be primarily due to infection.

Conclusions. 1. The successful autogenous kidney transplant in the neck of the dog functions for months in a practically normal manner, coëxisting with the normal kidney in the abdomen; it also maintains the life of the animal in good health for a fairly long time after the excision of the other kidney, while preserving its own functional activity. One transplanted kidney was in good condition four months after removal of the other kidney.

2. The neck can be used as a site for transplantation, and the kidney can be there utilized for the study of certain renal functions, as well as the physiologic activity of the transplant itself.

3. Analysis of chemical constituents of urine from the transplant as well as various functional tests made on it, simultaneously with the investigation of the remaining normal kidney in the abdomen or after the removal of this sister organ, shows a fairly normal kidney function.

4. An apparently compensatory activity of the transplant is observed after ablation of the other kidney.

5. The extrinsic nerve supply to the kidney and the ureter plays a minor and unessential part in their function, as the transplanted kidney functions equally well in the new location, and the renal pelvis and ureter show even an increased peristalsis.

6. The ultimate failure of the function of these autogenous kidney transplants, which have been transplanted successfully in the neck

and functioned a fairly long while, seems to be caused by hydronephrosis and infection, mainly incurred by mechanical insult in the new location.

7. These results of autogenous transplantation of the kidney may serve as a controlling experiment for renal transplantation of other kinds, such as the homogenous or heterogenous.

TABLE I.—CHEMICAL ANALYSIS OF BLOOD AND FUNCTIONAL TEST ON TRANSPLANT AFTER TRANSPLANTATION OF ONE KIDNEY AND EXCISION OF THE OTHER.*

Date, 1924.	Mg. for each 100 cc.			Percentage.		Output of phenolsulphonephthalein in first hour, per cent.	Comments.
	Non-protein N.	Urea N.	Creatinin.	Chlorids.	Sugar.		
Nov. 26	24	7.4	1.3	0.42	0.08	..	Before transplantation.
Dec. 1	...	.....	...	....	.....	4	
Dec. 8	...	.....	...	....	.....	13	
Dec. 11	21	6.6	1.2	0.49	0.07	..	Before excision of the other kidney.
Dec. 13	74	25.0	2.9	0.47	0.06	26	Good secretion from the transplant.
Dec. 26 1925.	73	17.0	1.7	0.49	0.07	30	
Jan. 11	..	17.3	1.6	0.47	0.07		
Jan. 14	222	117.6	...	0.36	0.16	Trace	Albumin, pus cells, casts in urine and uremic symptoms; animal died January 15, 1925.

* Transplantation of the kidney (Dog G-443) was performed November 26, 1924, and excision of the other kidney was performed December 11, 1924.

TABLE II.—CHEMICAL ANALYSIS OF BLOOD AND FUNCTIONAL TEST ON TRANSPLANT BEFORE AND AFTER EXCISION OF THE REMAINING KIDNEY IN THE ABDOMEN.*

Date, 1925.	Mg. for each 100 cc.			Percentage.		Output of phenolsulphonephthalein in first hour,† per cent.	Comments.
	Non-protein N.	Urea N.	Creatinin.	Chlorids.	Sugar.		
Jan. 19	32	5.2	1.3	0.45	0.08	..	Before excision of the other kidney.
Jan. 20	37	9.1	1.4	0.47	....	53	After excision of the other kidney.
Jan. 30	28	8.9	1.2	0.48	....	50	
Mar. 23	49	9.9	1.5	0.49	0.07	55	
April 5	52	13.8	2.1	0.52	0.08	51	
April 13	49	15.5	2.1	0.46	0.07	55	
April 20	42	4.3	1.4	0.50	0.07	..	
April 27	38	13.1	1.5	0.49	0.07	53	
May 4	34	5.9	1.7	0.48	0.08	53	
May 11	40	11.9	1.5	0.51	0.09	55	Pyelography of the transplant.
May 18	36	8.7	1.3	0.51	0.08	46	
May 20	28	10.4	1.3	0.47	0.08	..	Animal was killed by bleeding under ether.

* Transplantation of the kidney (Dog H-351) was performed July 14, 1924, and excision of the other kidney was performed January 19, 1925.

† It should be noted that the output of phenolsulphonephthalein from the transplant was 25 per cent and that from the other kidney 35 per cent before excision of the latter.

BIBLIOGRAPHY.

1. Carrel, A.: La technique opératoire des anastomoses vasculaires et la transplantation des viscères, Lyon méd., 1902, **98**, 859–864.
2. Carrel, A.: Doppelte Nephrektomie und Reimplantation einer Niere, Arch. f. klin. Chir., 1909, **88**, 379–411.
3. Carrel, A.: The Ultimate Result of a Double Nephrectomy and the Replantation of One Kidney, J. Exper. Med., 1911, **14**, 124–125.
4. Carrel, A. and Guthrie, C. C.: Functions of a Transplanted Kidney, Science, 1905, **22**, 473.
5. Dederer, Carleton: Studies in the Transplantation of Whole Organs. I. Autotransplant of the Left Kidney to the Neck with Right Nephrectomy in the Dog, J. Am. Med. Assn., 1918, **70**, 6–9.
6. Guthrie, C. C.: Bloodvessel Surgery, London, Edward Arnold, 1912, 360 pp.
7. Holloway, J. K.: The Effect of Diuretics on Transplanted Kidneys, J. Urol. (In press.)
8. Williamson, C. S.: Some Observations on the Length of Survival and Function of Homogenous Kidney Transplants, J. Urol., 1923, **10**, 275–287.

FUNCTION OF THE HOMOGENOUS KIDNEY TRANSPLANT.

By Kenji Ibuka, M.D.,

special student, the mayo foundation, rochester, minn.

(From the Division of Experimental Surgery and Pathology, The Mayo Foundation, Submitted for Publication July, 25 1925.)

Since many experimental studies proved that autogenous transplantations of the kidney could be made successfully, the attempt has been made, in anticipation of the clinical application of the operation, to replace disabled kidneys by the transplantation of others with normal function.

There are two sources of material for transplants for this purpose: One the homogenous and the other the heterogenous. The heterotransplant may be the more favorable source from the clinical point of view, as the homotransplant is not very convenient, not only because the sacrifice of a valuable organ risks the vitality of the donor, but also because the difficulty of securing such a transplant is greater under any circumstances. Nevertheless, heterogenous transplantation of the kidney has never been successfully accomplished because there are certain limitations and complicated biologic relationships between the donor and the recipient which are still unknown.[17, 18] While homogenous transplantation of the kidney is not so limited as heterogenous in this respect, decided success has not as yet been positively obtained, and many phenomena still remain obscure.

The present experimental study investigates the functional process of the homotransplant and its effect on the recipient. Before details are discussed the results and opinions of previous workers in this line and the hitherto unsolved problems will be reviewed.

Review of Previous Work. The first report of the homogenous transplantation of the kidney through the anastomosis of bloodvessels was made by Ullman and Decastello in 1902; they observed the excretion of urine from the transplanted kidney in the dog. Later, Floresco, Carrel and Guthrie, Capelle, Carrel, Unger, Borst and Enderlen, Guthrie, Villard and Tavenier, Villard and Perrin, Ingebrigsten, Dederer, Williamson, Holloway and Avramovici published the results of their investigation. Many of these investigators experimented with the autogenous transplantation of the kidney at the same time, in order to establish controls for the study of homogenous transplantation. Floresco, Carrel and Guthrie directed their investigations especially toward the establishment of surgical technique for this purpose, endeavoring to ascertain the proper site for the transplant, to improve methods for anastomosing bloodvessels, or to secure the appropriate management of the ureter of the transplant; Carrel's results were the most valuable. The dog and the cat were both used in these studies. As for the site for the transplant, every location that had been used in the autogenous transplantation was employed, such as the neck, the inguinal region and various sites in the abdomen. During the progress of the investigation of homogenous transplantation a special operation, called mass transplantation of the kidney, was worked out by Carrel and Guthrie, in order to study more closely the reconstruction of the urinary system and the functional efficiency of the homotransplant. They found in the simple transplantation certain mechanical troubles which made the experiment unsuited for use in investigation, but in subsequent researches both simple and mass transplantation of the organ were employed. The purpose of these studies was not only to demonstrate the possibility of homogenous transplantation of the kidney, but to compare the length of survival of such a kidney transplant or the life of the animal after transplantation, as well as the functional behavior of the transplant and the general condition of the recipient, with the results of similar studies on autogenous transplantation.

Concerning the length of survival and function of the homotransplant, Floresco observed that the homotransplants in the neck functioned for periods of from two to nine days, after which in every case they were destroyed by infection and necrosis. Dederer, who transplanted a kidney from one dog into the neck of another dog of the same litter, found that the homotransplant continued to function twenty-six days after operation, at the same time with the recipient's own kidneys, until the recipient died from intercurrent distemper. But this was regarded as rather a special case, as the transplantation was carried out between animals of close kinship. Williamson, who investigated this subject more thoroughly than the previous workers, comparing the length of survival and function of the autotransplant and homotransplant in the neck of the dog,

found that the homotransplant functioned for periods of from one to ten days (an average of four days), while the autotransplant functioned for several months, maintaining the life of the animal in a practically normal manner even after removal of the remaining normal kidney. The ultimate failure of the functional activity of the autotransplant was found to be caused by atresia of the ureter and hydronephrosis with a complication of infection, while that of the homotransplant was not due to such mechanical factors. Borst and Enderlen also found similar differences between the autotransplant and the homotransplant. They performed both transplantations with the same technique and in the same site in the abdomen, using the splenic bloodvessels for anastomosis to the renal artery and vein. The length of survival of the homotransplant was fourteen days, after which the kidney was in a necrotic condition, whereas the autotransplant functioned and maintained the life of the animal for one hundred and eighteen days with persistence of the normal renal structure. Such a difference in the length of survival of the two transplants was also evident in the results of other workers (Dederer, Villard, Carrel and Guthrie), although the comparison between autogenous and homogenous transplantation was not the purpose of their studies. As the result of mass transplantation, in which case the life of the animal depends on the functional activity of transplanted kidneys, Carrel and Guthrie found the shortest length of life after operation to be three days and the longest thirty-six days (average of sixteen days), at the end of which time the animals died from hydronephrosis, intestinal compression by peritoneal adhesion, phlegmon, puerperal infection, or compression of the renal vein by the connective tissue of organized hematomas. Unger, who also performed many experiments on cats and dogs, obtained no better results than Carrel. The longest time of survival among his animals was eighteen days after transplantation in one case; all the others died within shorter periods. The causes of death were thrombosis of the aorta and vena cava, peritonitis, postoperative hemorrhage, or diseases that, although obscure, did not seem to be uremia. Avramovici kept an animal alive seventy-one days, but other investigators also observed that the length of life of an animal after transplantation was short, eighteen days being the longest period observed by Borst and Enderlen, and twenty-four days by Ingebrigsten.

Carrel found fairly normal structure in some cases of transplanted kidneys, and in others the picture of interstitial nephritis. Borst and Enderlen, on the other hand, observed remarkable degenerative changes and necrosis of renal tissue, and Ingebrigsten a pronounced picture of acute nephritis with lymphocytic infiltration in the homotransplants. Carrel and Guthrie, investigating the functional efficiency of the homotransplant, observed in the mass transplantation experiments slight variations in the composi-

tion and total amount of the urine. All such variations, however, were entirely within normal limits, except the presence of coagulable protein, but the result obtained by Williamson, who tested the excretion of phenolsulphonephthalein from the transplant, and determined the nitrogenous elements in the blood of the recipient, established the fact that for a few days the homotransplant functioned similarly to the autotransplant, after which its activity failed. While all three kidneys were functioning, however, a sharp reduction was noticed in the nitrogenous elements of the blood urea and creatinin in the recipient. Holloway, who studied the influence of diuretics on the excretion of autotransplants and homotransplants, arrived at the same conclusion as Williamson.

Thus, from a general review of previous investigators, one perceives that conclusive success with transplantation of the homogenous kidney was not attained by previous workers, although the possibility of such transplantation and a certain amount of functional activity of the homotransplant were assured. The most marked fact observed by previous investigators is the difference in the length of survival and in the functional efficiency between the autogenous and the homogenous transplants. The length of survival of the homotransplant varied greatly, according to the different investigators, although they employed practically the same technique which they had previously established for autogenous transplantation, and which had been attended by good results in establishing the control for the experiment of homogenous transplantation.

Certain investigators attributed the different results and the varying behavior of autogenous and homogenous kidney transplants mainly to imperfection in surgical technique, such as interruption of the circulation, perfusion of the organ during the operation, or to mechanical factors, such as thrombosis of the bloodvessels, obstruction of the ureter, or else to infection after transplantation, to which the autotransplant also is subject, although to a lesser degree than the homotransplant. On the other hand, other investigators accounted for the divergencies in the results not so much by such surgical or mechanical factors, as by the fundamental biologic differences existing between donor and recipient.

The histologic picture and the functional efficiency of the transplant which were observed by the workers at different times after transplantation also resulted variously, and, in consequence, their interpretation differs widely. According to some investigators, the functional efficiency, as determined by frequent urinalysis and by observation of the general condition of the recipient, remained normal until the animal succumbed to intercurrent disorders, and wherever the function was modified in some measure they attributed it to errors in technique or other mechanical factors. They applied the same interpretation to the findings in the histologic

pictures of the homotransplants, some of which were nearly normal; in others which showed some interstitial and epithelial lesions they attributed the pathologic changes to perfusion, denervation or imperfect restitution of the anastomosed bloodvessels or of the ureter. Other workers, finding similar variations, were inclined to attribute these changes mainly to the biologic factor. The divergent results and opinions of previous investigators suggest that there are two phases of the experiment to be determined preliminary to the solution of the problems of transplantation. One is the investigation of the general underlying principle of biologic relationship between the donor and the recipient in transplantation, which may not be restricted to the scope of transplantation alone, and the other is a further attempt to improve technique and an exact comparison of the behavior of the autotransplant and the homotransplant by functional and histologic examination, considering the effect on both transplant and recipient.

Operative Technique and Method of Observation. The operative and routine procedures of these experiments were exactly the same as given in the preceding paper,[15] except, of course, that the transplanted kidney was obtained from another animal than the recipient. Fourteen homogenous transplantations of the kidney were done. Two of these were technical failures; four other experiments were complicated by postoperative sequelæ; eight of the experiments were technically successful in every respect.

Results of Experiments. The surgical technique of the operation of the homogenous transplantation was no more difficult than that of the autogenous. On the contrary, it seemed rather easier to carry out, as an adequately-sized kidney transplant could be obtained by choosing the donor, and the nephrectomy for obtaining the transplant in the same animal through laparotomy was not necessary; the animal therefore sustained less operative trauma and recovered more quickly from the immediate effect of the operation than after autogenous transplantation. The postoperative sequelæ, such as thrombosis of the anastomosed bloodvessels, obstruction of the ureter and infection of the transplanted organ, also were encountered no more frequently than after the autogenous transplantation, if the same technique and caution were used. In twelve experiments in which homogenous transplantations were performed, and in which the functional efficiency of the transplant was determined by analyses of the urine and the anatomic condition of the transplant was determined by exploration, 4 cases were complicated by such postoperative sequelæ. Exploration revealed in 1 case an infarct affecting about one-sixth of the kidney, due to a thrombus in a small arterial branch; in 1 a partial occlusion of the renal vein by a thrombus on the suture line of the anastomosed vein; in 1 a kinking of the ureter due to the dislocation of the kidney in the muscle pocket, and in 1 a superficial infection of the transplant

which occurred a few days after the operation. These complications might occur with the same frequency in autogenous transplantation, in case of an accident during the operation or in the course of the postoperative treatment.

Aside from these circumstances, however, the duration, both of survival and of excretory function in the homogenous transplant, was not long. The period during which the excretion of urine from the transplant was observed in my experimentation ranged from twenty-eight to one hundred and twenty hours, an average of three days, after the transplantation. The exact length of survival was difficult to determine, but the transplant usually became necrotic or softened two or three days after the cessation of its excretory function. The remarkable fact observed in the homotransplant under such conditions was that the cessation of the excretory function of the transplant occurred in spite of the maintenance of the circulation through the organ and the establishment of free drainage through the ureter, as demonstrated by two experiments. To determine when the secretion ceased, and at the same time to obviate any possible interference of free drainage of the ureter due to occlusion of the inserted catheter, the latter was washed with sterilized physiologic salt solution or distilled water, or else the old catheter was exchanged for a new patent one. At the same time, a fairly large amount (200 or 300 cc.) of water or physiologic salt or glucose solution was given orally or intravenously, as it had been established that such solutions had a more or less diuretic effect on the kidneys of the recipient, as well as on the transplant. To ascertain whether the circulation through the transplant was being maintained an incision was made through the protruding ureter. As long as the circulation was maintained bleeding from the ureteral bloodvessels could be perceived, as the blood supply to the ureter of such a transplant came through a branch from the renal artery.

The methods just described are, to some extent, indirect, as they do not exclude such conditions as partial occlusion of the bloodvessels by thrombosis or stenosis. The catheterization of the ureter, also, may fail to sustain free drainage for a long period of time if there is kinking of the ureter. However, these methods were controlled and the real condition ascertained by subsequent exploration, the transplant being exposed in its new site and the specimen dissected for direct inspection of the anatomic condition. At this exploration any dislocation of the transplant or kinking of the ureter would have been readily seen. The maintenance of the circulation could also be ascertained by examining the pulsation of the renal bloodvessels, and the enlargement and tenseness of the kidney under compression of the vein.

Regarding infections of the transplant, a most likely occurrence in animal experimentation of this kind, the same postoperative

treatment and care were carried out as had been used in the cases of successful autogenous transplantation. In many cases of autogenous transplantation of the kidney, however, even when a superficial infection of the wound and the transplant had occurred, the kidney had continued to function in the new location if no mechanical difficulty in the blood supply or the drainage of excreted urine arose. On the other hand, in the homogenous transplantation the organ nearly always ceased to function before any apparent sign of infection of the wound or of the transplant itself appeared. With regard to this last point, I am inclined to the view that such infections were not the real cause of the cessation of function and the failure of the transplant to heal in the new location.

The function of the homotransplant followed a different course from that of the autotransplant, just as the length of functional activity and of survival varied in the two. Some similarity in function of the transplant of both kinds was observed. The beginning of the excretion of urine from the homotransplant was often perceived at the end of the operation, but the copious flow usually began a few hours later. The urine, collected and measured frequently for a certain period of time during the entire course of the experiments, showed the maximal rate of flow the first day, frequently amounting to more than 100 cc. (highest, 129 cc.) during one hour. The rate then decreased gradually or abruptly during the following days until anuria set in. The diuretic reaction of the homotransplants to the administered water, salt or glucose solution, was identical to that of the autogenous transplants. The findings coincide with those of Holloway. The concentration of the nitrogenous constituents and chlorids in the urine were low the first day, rose to the maximum the second or third day and then decreased gradually or abruptly in the same way as the quantity of urine diminished. The quantities of urine, as well as the absolute amounts and concentration of nitrogenous substances in the urine from the transplant and from the kidneys of the recipient, were greater in the latter than in the former. However, when the homotransplant was still in full activity the absolute amount, as well as the concentration of chlorids in the urine from the transplant, was larger than in the urine from the recipient's kidneys. Urine from the transplant was always alkaline in reaction at first, but later was not constant and was often acid, especially near the end of the functional activity of the organ. The chemical reaction of urine from the transplant and of that from the recipient's kidneys did not always coincide, even when the specimens were collected during the same period. Albumin in the urine from the transplant was found in most cases immediately after transplantation, then often disappeared for a time and again appeared with red blood cells, pus cells and occasional casts in the organized sediments, when the quantity of urine diminished.

Regarding the functional test on the transplant with phenolsulphonephthalein, the beginning of the excretion of this dye occurred two or three minutes after its intravenous injection. Although the output during the first hour varied according to the excretory activity of the transplant, it sometimes reached 21 per cent, and followed a course parallel to the transition of excretion of nitrogenous constituents, showing the same relation to the urine from the recipient's kidneys as previously described, except that the concentration of the dye excreted in the urine from the transplant was sometimes more pronounced than that of the recipient's bladder urine. After the subcutaneous injection of phlorizin sugar appeared in the urine from the transplant as well as in the recipient's bladder urine, but the total amount of sugar excreted by the transplant was always smaller than that by the recipient's kidneys. Lithium carmin was excreted by both the transplant and recipient's kidneys after intravenous injection.

As to the effect of the homogenous transplantation on the recipient itself, the animal showed exteriorly no marked change in its general condition, but the routine examination of the constituents of the blood before and after transplantation, as well as after removal of the transplant, disclosed some apparent change in them. The blood urea nitrogen decreased more or less (to as little as 2.95 mg. for each 100 cc.), while the transplant was functioning well and the nonprotein nitrogen and creatinin also showed some decrease at times, as had been noted by Williamson in his experiments, except that their decrease paralleled that of the urea nitrogen (Fig. 1). No marked change of the chlorids and sugar in the blood was observed. It would have been desirable also to examine the change of total excretion of nitrogenous substances from the animal for the entire course of the experiment of homogenous transplantation, but this could not be carried out under the conditions of the present experiment. However, in the functional test with phenolsulphonephthalein, which may in some measure serve this purpose, it was repeatedly observed that the amount of dye excreted during the first hour, both by the transplant and the kidneys of the recipient, was larger than that by the latter alone, while the transplant was functioning well and the urea content of blood showed the lower level. After transplantation of the kidney the neck of the animal always showed gradual swelling, coinciding with the diminution of excretion, although without any apparent sign of infection of the wound or the transplant itself. Exploration at this stage usually revealed a marked accumulation of serous bloody fluid in the muscle pocket, excessive edema of the surrounding tissues and skin and enlargement of the kidney, even when the circulation was still maintained and the drainage of the ureter free. The kidney when removed under such conditions was apparently increased in size as well as in consistency, being sometimes swollen to nearly twice its

original size. The fibrous capsule stripped easily from the surface of the parenchyma, and the surface of the parenchyma usually looked smooth, but was mottled red and gray. On section the renal tissue was very edematous and swollen, and had lost its normal transparency. The cortex had a grayish color, the medulla appeared congested and the fine renal structure in both cortex and medulla was often indistinct. The pelvis was sometimes slightly distended and its mucous membrane edematous, but usually there was no apparent sign of infection. The ureter was also swelled with edema. The anastomosed bloodvessels were patent and clean on the suture lines and free from thrombosis. However, this change of the transplant, as well as of the surrounding tissues, might vary

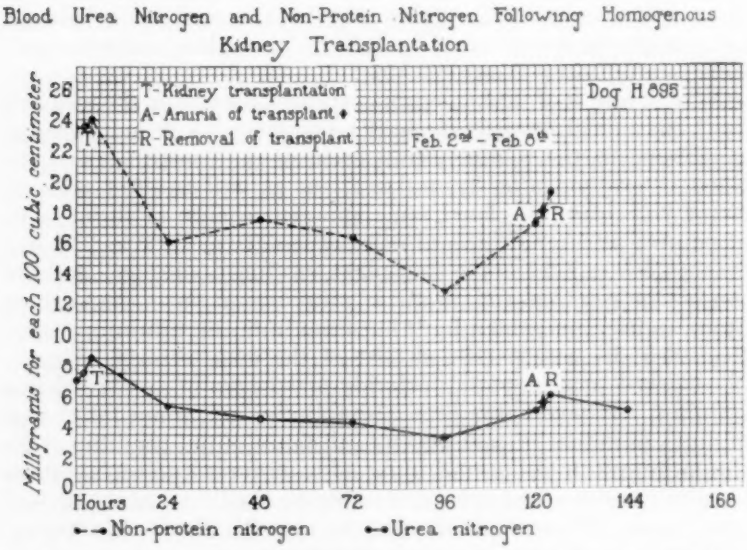

FIG. 1.—Chart showing blood urea nitrogen and nonprotein nitrogen following homogenous transplantation of the kidney.

in grade and intensity in each case and also with the different periods of time that had elapsed after transplantation. If the transplanted kidney was removed while it was still functioning fairly well it did not present such a marked picture of nephritis, but instead a cloudy swelling or degeneration of the parenchyma of varying degree. These macroscopic findings were confirmed microscopically. The kidney transplants which were removed soon after transplantation usually showed the picture of nephrosis, that is, desquamation and coarse granulation or fatty degeneration of the tubular cells, especially those of the proximal convoluted tubules and the thick limb of Henle's loop (Fig. 2). Many casts were observed in the thin limbs of Henle's loop and in the collecting

FIG. 2.—Photomicrograph of section from a homotransplanted kidney which was removed when it was actively functioning, seventy-two hours after transplantation. Marked desquamation and degeneration of tubular cells (Dog H-604) (× 120).

FIG. 3.—Photomicrograph of section from a homotransplanted kidney which was removed when it had shown marked decrease of excretion of urine, sixty-four hours after transplantation. Moderate degeneration of tubular cells, the glomeruli appearing fairly intact. Slight interstitial infiltration. (Dog H-200) (× 120).

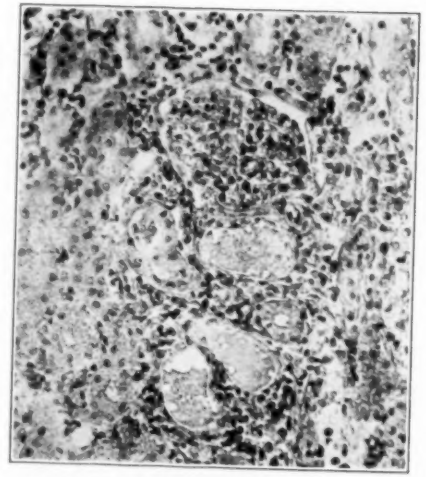

FIG. 4.—Photomicrograph of section from a homotransplanted kidney which was removed after development of anuria, but with circulation through it intact. Specimen obtained one hundred and twenty hours after transplantation. Marked degeneration of tubules as well as of glomeruli; some casts; interstitial infiltration with leukocytes and small round cells. (Dog H-895) (× 120).

tubules, but without evidence of damage to the glomeruli (Fig. 3). However, very soon after this metamorphosis of the tubular cells infiltration of leukocytes and small round cells around glomeruli and bloodvessels in the parenchyma began, and increased gradually until the process spread throughout the interstitium of the renal tissue, but not to any marked extent in the lumen of the tubules. The glomeruli and tubules revealed at the same time progressive damage of their structure, even to fatty degeneration of glomerular tufts and necrosis of tubular cells (Fig. 4).

Discussion. This series of experiments established two facts: (1) That the period of survival of the homotransplant was short as compared with that of the autotransplant; (2) that the functional behavior of the two kinds of transplants presented certain marked differences. Whether the ultimate cause of these differences lies in the surgical and the allied mechanical factors, or in the biologic factor, must now be considered.

Observations made during this study do not support the conclusion that imperfections of surgical technique lie at the root of the differences in the length of survival and in the functional behavior of the two kinds of transplants. The same surgical technique and postoperative treatment were employed that had led to successful results in previous experiments with autogenous transplantations of the kidney into the neck of a dog. The autotransplant in this site had functioned for months in a practically normal manner, both before and after removal of the remaining normal kidney, and had maintained the animal in good health as long as the activity of the transplant had continued. But the homotransplant, although the same methods were used, failed to heal well in the new site, or to survive as long as the autotransplant. Likewise the duration of the functional activity of the homotransplant was short (a maximal of six days and an average of three) as compared with that of the autotransplant, which had continued more than ten months. The homotransplant functioned similarly to the autotransplant for a short time, but very soon failed to function as proved by chemical analysis of the urine, and functional tests on the organs, as well as by histopathologic examination of the specimens themselves. The failure of the homotransplant to heal well, to function long, or to survive for any length of time, led me to exclude the surgical and mechanical factors as the real cause of failure.

Some investigators, notably Unger, had performed homogenous transplantation in certain cases without the removal of the recipient's kidneys, and, finding disability and marked histologic (nephritic) changes in most of these transplants, had attributed them to the lack of functional demand on the homotransplants, since the physiologic function could be carried out sufficiently by the recipient's kidneys alone. I had previously ascertained that the auto-

transplant functioned well in the new location, coëxisting with the remaining kidney in the abdomen for a fairly long period (more than six months). In the present series of experiments the homogenous transplantations were also made without the removal of the recipient's kidneys, but the homotransplants were placed under such conditions that they had to function with the kidneys of the recipient. The results showed that the homotransplant, like the autotransplant, functioned with the recipient's kidneys, reducing the nitrogenous constituents of the blood, and probably eliminating more urinary constituents than were excreted by the recipient's kidneys, when the latter were in full activity. Furthermore, two other cases were observed which corroborated these results. In each of the latter one kidney from the donor was transplanted into the neck of the recipient, immediately after which, in 1 case one of the recipient's kidneys, and in the other case both, were removed. The length of survival and the functional behavior of the transplants were then ascertained by means of the collection and chemical analysis of the urine, the functional test of the kidney with phenolsulphonephthalein and the determination of the blood urea and nonprotein nitrogen. The transplants in these cases, however, showed no marked differences either in the length of survival or in functional behavior, when compared with those of the homotransplants which had been present with the recipient's own kidneys. Such considerations tend to indicate that the lack of functional demand as the cause of failure in homogenous transplantation should be excluded.

After considering the results of homogenous transplantation of all other kinds,[17, 18] which generally ended in much the same manner, the conclusion was reached that the failure of the homogenous transplantation of the kidney is chiefly due to biologic factors. Into these factors, according to many investigators,[2, 17, 19] may enter various elements, such as individual difference in cell protein, inequality of serum in osmotic relation and so forth, or such manifestations of these elements in the living organism as the toxic effect of foreign protein on the recipient, or the anaphylactic reaction of the recipient's body on the transplants.

Summary. Homogenous transplantation of the kidney was performed and studied in fourteen pairs of dogs, the same surgical technique and postoperative treatment being carried out as in the autogenous transplantation of the kidney previously studied and reported. No special consideration was given to the breed of, or relationship between, donor and recipient.

The function of the homotransplants in the neck, present with the kidneys of the recipient, was observed. This was found to continue for a few days (an average of three days) after transplantation and to end by necrosis or softening of the transplant shortly after the cessation of its function.

Chemical analysis of specimens of urine and functional tests on the transplanted kidney proved that the homotransplant functioned similarly to the autotransplant for a limited time, but the function soon changed and finally ceased, contrary to the behavior of the autotransplant, which had recovered and assumed normal function at the corresponding period when the homotransplant failed.

In the functional tests with phlorhizin, carmin and phenolsulphonephthalein the excretion of sugar and these dyes was observed in the specimens of urine from the homotransplant as well as from the recipient's kidneys. The test with phenolsulphonephthalein on the homotransplant showed that the elimination of the dye from the transplanted kidney varied according to nitrogenous constituents of urine from it, and the total amount of this dye eliminated by three kidneys during the first hour after injection was apparently greater than that eliminated by the recipient's kidneys alone before operation.

While all three kidneys were functioning the nitrogenous constituents of the blood were reduced, but the chlorids and sugar in the blood were not changed. The urea nitrogen showed the most marked reduction, but the nonprotein nitrogen and creatinin also were decreased.

The macroscopic, as well as microscopic, examination of the specimens of the homotransplant revealed that the transplanted kidneys were affected at first by nephritic changes of the parenchyma, such as cloudy swelling and degeneration of the tubular elements, and then by marked nephritic processes in the renal tissue, showing profound degeneration of glomerular and tubular elements with extensive interstitial infiltration of leukocytes and small round cells.

TABLE I.—CHEMICAL ANALYSIS OF SPECIMENS OF URINE FROM THE TRANSPLANT AND THE BLADDER OF THE RECIPIENT COLLECTED DURING THE SAME PERIOD.*

(Recipient, Dog H-200; donor, Dog G-789.)

	Volume, cc.	Color.	Reaction.	Albumin.	Total nitrogen mg.	Urea and ammonia nitrogen mg.	Ammonia nitrogen, mg.	Chlorid mg.	Phenolsulphonephthalein excretion, first hour.
Transplant	25	Clear yellow	Neutral	Positive	58.25	41.00	1.65	6.90	21 per cent in 41 cc
Bladder	39	Clear light yellow	Slightly acid	Negative	226.20	189.90	7.80	5.77	43 per cent in 111 cc.

* Between 1.40 and 2.25 P.M. November 27, 1924.
Transplantation had been performed twenty-five hours previous to the time of securing these specimens.

This great difference in the length of survival and in the functional behavior of the homotransplant, as compared with the autotransplant, in the experimental operations which were performed in the same manner, cannot be attributed simply to the surgical or mechanical factors of the operation, but probably is due to some underlying biologic factor in homogenous transplantation, which is not as yet understood.

TABLE II.—CHEMICAL ANALYSIS OF THE BLOOD OF THE RECIPIENT FOLLOWING HOMOGENOUS TRANSPLANTATION OF THE KIDNEY.
(Recipient, Dog H-871; donor, Dog H-872.)

Date, 1925.	Time.	Mg. for each 100 cc.		Comment.
		Nonprotein N.	Urea N.	
Jan. 26	8.30 A.M.	25.0	6.6	Before operation.
	10.20 A.M.	....	....	Transplantation satisfactorily finished.
	11.50 A.M.	17.5	6.4	Secretion fairly good.
	4.50 P.M.	14.4	3.7	Secretion good, output of phenolsulphonephthalein during the first hour after injection 18 per cent in 129 cc. of urine from the transplant.
Jan. 27	8.30 A.M.	22.0	3.2	Secretion very good. Phenolsulphonephthalein, 20 per cent in 59 cc.
	11.55 A.M.	20.0	4.4	Secretion good.
	4.45 P.M.	19.5	6.45	Secretion fairly good.
Jan. 28	8.35 A.M.	12.6	4.2	Secretion decreased.
	11.30 A.M.	21.6	3.1	Secretion markedly decreased.
	4.40 P.M.	14.8	4.5	Phenolsulphonephthalein trace in 3 cc.; secretion almost ceased.
Jan. 29	8.35 A.M.	....	5.6	Anuria.
	4.50 P.M.	....	6.6	Transplant removed five hours before.

BIBLIOGRAPHY.

1. Avramovici, A.: Les transplantations du rein (étude experimentale), Lyon chir., 1924, **21**, 734–757.

2. Borst and Enderlen: 2. Transplantation von Nieren, Deutsch. Ztschr. f. Chir., 1909, **99**, 135–163.

3. Capelle: Ueber Dauerresultate nach Gefäss-und Organtransplantationen, Berl. klin. Wchnschr., 1908, **45**, 2012–2013.

4. Carrel, A.: Transplantation in Mass of the Kidneys, J. Exper. Med., 1908, **10**, 97–140.

5. Carrel, A.: The Ultimate Result of a Double Nephrectomy and the Replantation of One Kidney, J. Exper. Med., 1911, **14**, 124–125.

6. Carrel, A. and Guthrie, C. C.: Anastomosis of Bloodvessels by the Patching Method and Transplantation of the Kidney, J. Am. Med. Assn., 1906, **47**, 1648–1651.

7. Carrel, A. and Guthrie, C. C.: Successful Transplantation of Both Kidneys from a Dog into a Bitch with Removal of Both Normal Kidneys from the Latter, Science, 1906, **23**, 394.

8. Decastello, A. von: Ueber experimentelle Nierentransplantation, Wien. klin. Wchnschr., 1902, **15**, 317.

9. Dederer, C.: Homotransplantation of the Kidney and Ovary, Surg., Gynec. and Obst., 1920, **31**, 45–51.

10. Floresco, N.: Transplantation des organes, J. de physiol. et de path. gén., 1905, **7**, 27–46.
11. Guthrie, C. C.: Survival of Engrafted Tissues, J. Am. Med. Assn., 1910, **54**, 831–834.
12. Guthrie, C. C.: The Effect on the Kidneys of Temporary Anemia, Alone and Accompanied by Perfusion, Arch. Int. Med., 1910, **5**, 232–245.
13. Guthrie, C. C.: Bloodvessel Surgery, London, Edward Arnold, 1912, 360 pp.
14. Holloway, J. K.: The Effect of Diuretics on Transplanted Kidneys, Jour. Urol., (In press.)
15. Ibuka, K.: Function of the Autogenous Kidney Transplant, Am. J. Med., Sci., 1926, **171**, 407.
16. Ingebrigsten, R.: Homoioplastische Nierentransplantation, Zentralbl. f. Chir., 1914, **2**, 1740.
17. Lexer, E.: Die freien Transplantationen, Neue deutsche Chirurgie, Stuttgart, F. Enke, 1919–1924, vol. **26**.
18. Neuhof, Harold: The Transplantation of Tissues, New York, D. Appleton and Company, 1923, 297 pp.
19. Schöne, G.: Die heteroplastische and homoöplastische Transplantation, Berlin, J. Springer, 1912, 161 pp.
20. Ullmann, E.: Nierentransplantation, Wien. klin. Wchnschr., 1902, **15**, 707.
21. Unger, E.: Ueber Nierentransplantation, Berl. klin. Wchnschr., 1909, **1**, 1057–1060.
22. Unger, E.: Nierentransplantation, Berl. klin. Wchnschr., 1910, **1**, 573–578.
23. Villard, E. and Perrin, E.: Transplantations rénales, Lyon chir., 1913, **10**, 109–134.
24. Villard, E. and Tavenier, L.: La transplantation du rein, Presse méd., 1910, **18**, 489–492.
25. Williamson, C. S.: Some Observations on the Length of Survival and Function of Homogenous Kidney Transplants, J. Urol., 1923, **10**, 275–287.

RENAL SEPSIS ASSOCIATED WITH MANIC DEPRESSIVE INSANITY.[1]

By Edward F. Kilbane, M.D.,
NEW YORK.

In view of the fact that reports of surgical procedures for the removal of foci of infection in patients suffering also from mental affections have occupied a considerable space in recent medical literature, it has seemed worth while to the writer to report the case here recorded.

The abstract of her history as received from Bloomingdale Hospital covering the period from the onset of her trouble to her discharge from that institution is as follows:

The patient, aged forty-two years, was born in the United States. Her family history is irrelevant: there is no knowledge of any nervous or psychotic disorder and her childhood and girlhood were entirely without incident connected with her present condition. After her marriage she had sufficient domestic help to relieve her of most of the usual household duties, but she had few interests and few friends. She did not dance or play cards, and, while she attended

[1] From the Roosevelt Hospital.

and enjoyed the theater, her life was otherwise pretty much of a routine of household duties, but apparently one of entire contentment to the patient. Her general health was always quite well with no ills other than a tendency to frequent attacks of flatulence.

Her menstrual history is negative. During early married life contraceptive measures were employed but later there was some desire on the part of the patient for children, and, although more recently pregnancy had not been expected she was at first alarmed and then delighted, when in 1921 it was found that she was pregnant. During the early period of the pregnancy there was slight nausea but she ate and slept well and her general health remained very good throughout her pregnancy. She was delivered of a male child in August, 1922, the delivery being instrumental but not exceedingly difficult and she afterward made an uneventful convalescence.

Her present illness became noticeable almost immediately after getting out of bed after her confinement, at which time she began to get nervous, complained of cardiac palpitation and imagined she had heart trouble.

About October 1, two months after her confinement, she complained of pains in her abdomen and across her back and at this time a diagnosis of bilary colic was made; these symptoms disappeared, however, after she had passed two small urinary calculi. By this time her nervousness had increased considerably and she complained much of cardiac palpitation and was extremely apprehensive about her heart and her health. She also had many crying spells and could not sleep without the aid of hypnotics and from this time on required the constant attention of a nurse.

It was found that she was better when she kept away from her baby, so artificial feeding was substituted for nursing and it was also noted that her condition was worse when she had visitors, she herself complaining that the latter bothered her. When her husband tried to have her do various things with the idea of promoting enjoyment for her she complained that he was trying to test her but would offer no explanation as to the nature of the testing she suspected. She had occasionally threatened suicide, stating that she was of no use in the world and only a burden to her family, and had on occasions held a knife or fork in her hand and pretended to injure herself. Principally because of these actions she was admitted to Bloomingdale Hospital on February 20, 1923, her family feeling that it was impossible to take adequate care of her at home. In the hospital the patient was frequently tearful and complained that she wanted to get out as she was worried about her baby. She admitted that she had talked of suicide, but said that she would not have done it, and she denied any real attempt at it.

While she was under observation in the hospital there was no evidence of hallucinations; no delusions could be elicited; the patient

was well oriented and without memory defects; her memory retention was good and her general intelligence was average for her social condition. Calculation was only fair, her repetition of numbers was poor, and her insight was partial. The patient stated that she felt quite upset about things not being right and admitted she was extremely nervous and apprehensive.

The general physical examination at this time showed a well-developed, fairly well-nourished woman, aged forty-two years, 5 feet 1 inch in height and weighing 119 pounds, with an essentially normal temperature, pulse and respiration.

Laboratory findings were as follows: Urinalysis was negative in the beginning, but in July there was quite a large quantity of albumin, which, however, did not persist. A Roentgen ray examination of her mouth showed badly infected teeth. The blood Wassermann was negative, and the blood cell and differential white cell counts were normal.

On June 4 she complained of pain in her left side and in her back. This was attended by a slight rise in temperature, and on June 28 this condition was repeated, the rise in temperature disappearing after colonic irritation in each instance.

On July 21, following another attack of pain, there was some tenderness and a sense of a mass in the left loin, and, on the suspicion of a kidney lesion, the phenolsulphonephthalein test was done and gave 32 per cent elimination in one hour and 47 per cent in two hours. As there was no pus in the urine at this time and a total absence of chill or fever in any attack it was presumed that there was little evidence of pyonephrosis, although it was thought that there might be a possibility of a hydronephrosis.

A Roentgen ray of the gall bladder was taken with negative results, the plate showed a rounded shadow opposite the third lumbar vertebra in the region corresponding to the pelvis of the left kidney.

On July 26, 1923, she was discharged from Bloomingdale Hospital, the discharge diagnosis being manic depressive insanity; depressive type (puerperal) and her condition noted as improved during her stay in that institution. She was admitted to Roosevelt Hospital on the following day to the writer's service. On the admission sheet the notation was made that the patient is a well-developed woman apparently not ill physically, but extremely nervous and agitated. The general physical examination elicited little of importance except that the left kidney was ptosed. The urine was turbid, contained a trace of albumin, no sugar, and the microscopic examination showed hyaline casts, calcium oxalate crystals, pus cells and red blood cells.

Blood analyses showed: Urea nitrogen, 15.9 mg.; creatinin, 1 mg.; uric acid, 5 mg.; sugar, 125 mg. per 100 cc. of plasma. The Wassermann examination was repeated and again the reaction was negative.

Cystoscopic examination showed the bladder tolerance and bladder capacity normal, although the bladder mucosa was congested and the walls trabeculated and there was much pus floating about in the distending fluid. The left ureteral orifice was distinctly congested. A catheter passed up the left ureter readily, no obstructions being noted. The flow of urine began immediately and was rapid and continuous without the intermissions normally present and the urine was turbid in appearance. One ounce of residual urine was aspirated from this pelvis, the last portion obtained being thick pus. Culture of the urine from this kidney showed a growth of Staphylococcus albus. The capacity of this pelvis for injected fluid was measured and found to be greatly increased above normal. A roentgenogram showed a shadow, evidently that of a calculus in the region of the left pelvis in close apposition to the shadow of the catheter. (Fig. 1.) A pyelogram showed a marked distention of the pelvis and calices but with a definite periphery of kidney tissue remaining, and the kidney was ptosed and rotated downward and the course of the ureter tortuous. (Fig. 2.) A catheter passed to the right pelvis readily; the flow of urine was normally intermittent in character and rapid in rate and the urine was clear. Microscopic examination of this urine was negative and cultures remained sterile at the end of forty-eight hours. Both the phlorizin and the phthalein test for kidney function were used and the former found to be positive on the right side in twenty-two minutes but still negative on the left side at the end of fifty-two minutes when the examination was terminated. While phthalein appeared in the urine from the right kidney within four minutes, and in eight minutes from the left, the reaction was noted as being strong on the right side but very faint in the urine from the left kidney.

The cystoscopic diagnosis was: A ptosed left kidney with a dilated and infected pelvis, containing a calculus; probably a pyelonephritis with very poor function of this kidney. The chemical functional tests gave good reactions in the right kidney and would indicate that this kidney was capable of performing the entire renal function.

We had here demonstrated a calculus pyelonephritis in a patient suffering also with a serious mental disturbance and one of the important aspects at this time was to evaluate the causative relationship of the former to the latter. No other gross focus of infection was apparent and while sepsis may not be generally accepted as a cause of manic depressive psychosis, it seemed reasonable to suppose that the kidney condition might be in this instance an important etiologic factor. Moreover the kidney condition in itself warranted surgical intervention.

Under ordinary circumstances, careful consideration would be given to the advisability of a pyelotomy for removal of the calculus and a nephropexy to replace the kidney in its normal condition

FIG. 1.—Roentgenogram shows ptosed kidney, calculus in pelvis and tortuous course of the ureter.

FIG. 2.—Pyelogram showing the dilated pelvis and the dilated and blunted calices.

and correct the abnormal course of the ureter as the operation of choice, with the reservation, that if unsuccessful in freeing the patient of her symptoms, a secondary nephrectomy could be done. It would seem fair to state that the chance of saving the kidney by such a conservative procedure warranted the risk of a failure under ordinary circumstances. However after considering that the other kidney showed good functional reactions to the usual chemical tests, that the blood chemistry figures were normal and that an operation affording the most rapid and uncomplicated postoperative result promised both the least strain on the patient's already badly disorganized mental state and the maximum of physical benefit, a nephrectomy was decided upon.

Operation was performed on August 1, 1923, under gas and ether anesthesia, and without undue technical difficulty I removed the left kidney and upper ureter. The kidney measured 10 cm. by 6 cm. by 4 cm. and weighed 135 gm. There was a small hematoma beneath the capsule which otherwise appeared normal and stripped readily. No abnormalities were seen on the cut surface except a moderate redness of some of the apices of the pyramids. The pelvis contained a calculus and was dilated and its mucosa showed numerous petechial hemorrhages.

Microscopic examination showed the entire wall of the pelvis to be infiltrated with round cells which were generally collected into small clumps; it was much thickened in places; parts of the epithelium were absent and the capillaries injected. As for the kidney itself, the apex of a pyramid showed dilatation of the vessels and considerable hemorrhage and edema. At the junction of calyx and pyramid there was necrosis with lymphocytic infiltration and there were also small necrotic points diffusely scattered throughout the cortex with an accumulation of lymphocytes, the latter being especially numerous just beneath the cortex. Diagnosis: pyelonephritis and renal calculus.

After a study of the sections of the kidney there is grave doubt if anything short of removal of the organ would have been successful, and, disregarding entirely the mental condition of the patient, there is no question but that the nephrectomy was the best procedure.

The postoperative course in the first three days was very stormy. Much pain was complained of and as the patient reacted very badly to the administration of morphin, attempts at relief were confined to the administration of bromids and chloral, poor substitutes for morphin for relief of postoperative pain. She slept at short intervals only, and, just as before operation, the bedside notes consisted principally of notations to the effect that the patient was restless, nervous, depressed and crying. Considerable abdominal distention was present for the first three days but this responded to the usual measures. After a few days no further concern was felt as to her physical condition, and the surgical convalescence was thereafter uneventful.

Nine days after operation a definite change for the better was noted in the patient's mental condition and that night she slept well, her first good night in many months. She was allowed out of bed on the twelfth day and was bright and cheerful all day and thereafter, and three days later she was discharged to her home. From then until the present time, a period of about two years, her mental condition has been normal and her life exactly the same as before the onset of her illness. Her physical condition has been satisfactory and no treatment has been necessary except supervision of her diet to counteract a tendency to become obese.

Discussion. Inadvisable as it undoubtedly may be to draw conclusions from one case, it does seem justifiable in this instance to infer a very definite causative relationship between the infected kidney and the disturbed mental state, particularly when the manifestations of the latter, which had persisted for nearly nine months and were of such severity as to necessitate confinement in a hospital devoted to the care of insane patients, cleared up completely and permanently within fifteen days after removal of the septic kidney.

The question of accepting the accuracy of the diagnosis of manic depressive insanity may well be raised in looking at the case in retrospect. However, it must be remembered that that diagnosis was made by competent attendants after a period of observation extending over several months.

The question of the relationship of the puerperal state might also be raised. The onset of the psychosis soon after the confinement denotes a possible, even a close connection, but the persistence of the mental condition for such a long period afterward would seem to relegate this to a position of only secondary importance and make it appear that the infection of the kidney, which had undoubtedly been present, though without symptoms, for a long period, was the active and predominating etiologic factor.

Summary. The relationship between the serious mental condition of this patient and the infection of her kidney may have been quite accidental and her return to normal mentality after operation may also have been a coincidence; still, the possibility of a direct relationship justifies the reporting of this case as one in which the kidney condition was the important etiologic factor. Furthermore the results would seem to warrant a complete and careful urologic examination in mental cases in the presence of urinary sepsis and it would seem proper to grant these patients the benefits of corrective surgical intervention.

REVIEWS.

A Medical Formulary. By E. Quin Thornton, M.D., Assistant Professor of Materia Medica in the Jefferson Medical College, Philadelphia. Twelfth edition. Pp. 352. Philadelphia: Lea & Febiger, 1925. Price, $2.50.

This ever useful little book has become particularly desirable on account of the many changes caused by the appearance of the tenth edition of the *U. S. Pharmacopœia*. E. K.

Hand Atlas of Clinical Anatomy. By A. C. Eycleshymer, B.D., Ph.D., M.D., Dean of the College of Medicine and Director of the Department of Anatomy, College of Medicine, University of Illinois; and Tom Jones, B.F.A., Director of Anatomical Illustration and Instructor in Anatomy, College of Medicine, University of Illinois. Pp. 424; 395 illustrations. Philadelphia: Lea & Febiger, 1925. Price, $11.00.

This volume is an outgrowth of the work prepared for the Medical Corporation of the Army and Navy during the late war. It is divided into four parts: Part I, The Head and Neck; Part II, The Thorax, Abdomen and Pelvis; Part III, The Upper Extremity; Part IV, The Lower Extremity. The illustrations are excellent. They are arranged as: (*a*) Transparencies or projections; (*b*) systematic dissections; (*c*) regional dissections; (*d*) frontal, sagittal and transverse sections; (*e*) surgical incisions. A series of muscle projections showing the muscles in their relation to body outline and bony structures is unique and interesting. The index is good and is also explanatory which makes it doubly useful. For much of the material the authors are indebted to the authors of other well-known atlases. This book should be well received by surgeons, both special and general, as an easily available text for anatomic reference. I. R.

Traitement du Diabète. By Pedro Escudero, Professor of Clinical Medicine, University of Buenos Aires. Pp. 276. Paris: Norbert Maloine, 1925. Price, 30 francs.

A practical satisfactory statement of the management, not merely of diabetes, but of the individual patient. The book, how-

ever, gives the impression of having been hastily put through the press, nine of the two hundred and seventy-six pages being devoted to corrections and errata in the text. The American reader will not find anything not covered at least as well in the standard American works. R. K.

BAILEY'S TEXTBOOK OF HISTOLOGY. Revised and rewritten by OLIVER S. STRONG, A.M., PH.D., Associate Professor of Neurology, College of Physicians and Surgeons, Columbia University New York; and ADOLPH ELWYN, A.M., Assistant Professor of Anatomy, College of Physicians and Surgeons, Columbia University, New York. Seventh edition. Pp. 939; 585 illustrations. New York: William Wood & Co., 1925. Price, $7.00.

IN this seventh edition the chapters on the Cell, Epithelium, Connective Tissue, Cartilage and Bone, Blood and Muscle have been rewritten and expanded by the new authors; the chapters on Nerve Tissue and the Nervous System enlarged in a capable manner and many new illustrations added. Much the largest part of the book, over four hundred pages, is devoted to the Organs (Part III), this being preceded by a short Part I on the Cell and two hundred pages on the Tissues and followed by fifty pages of Histological Technique. The illustrations, for the most part, are good, especially the photographs of the Weigert preparations, reproduced by a new method. One misses references to original papers as well as any mention of the conductive system of the heart, the different cells of the islands of Langerhans, the Kupffer cells of the liver. In fact, the important recent development of the reticulo-endothelial system seems to have escaped the reviser's attention. On the other hand, the blood, the pituitary and other ductless glands are well presented. On the whole, the book can be heartily recommended. E. K.

SYMPTOMS OF VISCERAL DISEASE. By FRANCIS M. POTTENGER, A.M., M.D., LL.D., F.A.C.P., Medical Director, Pottenger Sanitarium for Diseases of the Lungs and Throat, Monrovia, Calif. Third edition. Pp. 376; 86 text illustrations and 10 color plates. St. Louis: C. V. Mosby Company, 1925. Price, $6.50.

THE author's treatise on the anatomy, physiology and pathology of the vegetative nervous system marks a step forward in the pioneering of that region where so much is known and so little correlated. The need among the profession for enlightenment such as the author furnishes is evidenced by the fact that this is the third edition in six years.

The presentation of the subject matter is much improved. In previous editions the anatomy was treated last, but now it assumes

its rightful first place. The section is at times hard reading, but very necessary to an understanding of the regional and general vegetative functions as revealed in the rest of the book.

The conception of exophthalmic goiter as a stimulation of the vegetative nervous system by toxic thyroid products will probably meet much opposition from the New York Mt. Sinai school and their followers, who feel that thyrotoxicosis is merely a further expression of, and an individual variation from, the regular picture of autonomic imbalance.

Monographs and textbooks are notably soon out of date, but we feel that nowhere else have we seen such accurate, concise and yet complete modern information on the vegetative system gathered into one work. C. L.

EYE, EAR, NOSE AND THROAT MANUAL FOR NURSES. By ROY H. PARKINSON, M.D., Visiting Oculist and Aurist to St. Joseph's Hospital, San Francisco, Calif. Pp. 207; 51 illustrations. St. Louis: C. V. Mosby Company, 1925.

THE author has especially had in mind the student nurse when preparing this book. It is clear, simple, practical and concise. Reproductions of pen and ink drawings make a valuable contribution. The first part of the book is devoted to a discussion of the general conditions which the student nurse will meet, the second part is devoted to operating-room technic and the third part deals with the relation of the public-health nurse to this field. Pertinent information is given to her which will aid her in solving many of the problems relating to the special senses with which she is in daily contact. S. G.

CLINICAL LABORATORY MEDICINE. A Textbook of Clinical Laboratory Diagnostic and Therapeutic Procedures. By HENRY M. FEINBLATT, M.D., Director of Laboratories, United Israel-Zion Hospital; and ARNOLD H. EGGERTH, A.B., A.M., Associate Professor of Bacteriology, Long Island College Hospital, Brooklyn, N. Y. Pp. 424; 87 engravings and 2 colored plates. New York: William Wood & Co., 1925. Price, $5.00.

THE sections on bacteriology are very good, with the exception of the mouse method of typing pneumococci, where omission of some important details diminish the accuracy of the presentation. Cultures should be made of the heart blood and the peritoneal exudate before washing out the cavity; agglutination tests should always be made with pure cultures. The chapter on Basal Metabolic Rate is rather too much condensed for the beginner. In blood chemistry the ordinary methods are included and are more simplified and workable for the beginner than is the case in most laboratory manuals. In clinical pathology the technic given for cross-

agglutination and for blood transfusion is too brief; no mention is made of reporting hemoglobin in grams or that in testing for occult blood in feces the patient should be placed on a meat-free diet.

In general, however, the descriptions of the methods given are concise and clear, the illustrations and print splendid, the index good and the references so placed in the body of the text as to stimulate interest in the subject. For a reference book in advanced laboratory work it is not sufficiently exhaustive; but will be of value to the beginning student and the practitioner, as much weight is given to the proper significance or interpretation of laboratory findings from the clinical point of view. W. C.

Midwifery Mechanics. By Lieut.-Col. Andrew Buchanan, I.M.S. (Rtd.), M.A., M.D., M.Ch., M.A.O., Ex-Superintendent of Nagpur Medical School and Dufferin Hospital. Pp. 82; 12 plates. London and Shanghai: Humphrey Milford, Oxford University Press, 1924.

In these days of mechanical obstetrics it is refreshing to note that someone is still interested in the natural physical processes concerned in parturition. This small book is an attempt to smooth out the difficulties experienced by the average student in understanding the mechanism of labor. By pictures, models, diagrams and text the "theory of the pivot points" is made clear. The large number of abbreviations and symbols is at first confusing. The book is not read with ease; it has to be studied. But a study will repay anyone interested in physics and dynamics of obstetrics. P. W.

Chronic Intestinal Stasis: A Radiologic Study. By Alfred C. Jordan, C.B.E., M.D. (Camb.), M.R.C.P. (Lond.), Corresponding Foreign Member, Belgian Royal Academy of Medicine. Pp. 230; 315 illustrations. London: Henry Frowde and Hodder & Stoughton, 1923.

The author has accepted in full the theories regarding intestinal stasis that have been advanced by Sir William Arbuthnot Lane and has assigned to this condition an important place in the causation of almost all bodily ills, from pyorrhea alveolaris to uterine retrodisplacement, Duputren's contraction and delusional insanity. Many statements are made with a preciseness and finality that are not justified. The book would have been more impressive if the discussion had been limited to the roentgenologic aspects of intestinal stasis. Even in this field, however, it invites criticism since many of the Roentgen-ray illustrations are only with difficulty reconciled with the legends which accompany them. T. M.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND.

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

The Diameter of the Red Blood Cells in the Differentiation of Anemias.—About four years ago Mr. Price-Jones brought out a very interesting article followed by other articles later on a study he had made on the measurement of the red blood cells. This work had been done by several previous observers, but their technic was not as simple nor did they evolve the interesting curves which were brought out by Price-Jones. At this time the author showed that in diseases of the hematopoietic system there are interesting changes in the size of the red cells which can be accurately determined. This finding, of course, is merely an exact quantitative estimation of the well-known fact that in pernicious anemia megalocytes and megaloblasts are common. GROSH and STIFEL (*Arch. Int. Med.*, 1925, **36**, 874) have simplified the technic of Price-Jones and have independently devised a method of measuring the diameter of the red cells which is a much more simple procedure than any methods as yet advocated. In a series of a considerable number of patients they found the following: The normal average diameter of the erythrocyte is 7.42 microns. In pernicious anemia the curve shows a marked tendency to be much greater, extending from 7 to 11 microns. This is a differential point in the diagnosis of this disease of value in differentiating it from malignancy, for example, in which the curves are to the left of the normal and differentiating this disease from posterior lateral sclerosis, which often resembles pernicious anemia so closely as to be thought to be the same disease.

The Value of the Icterus Index in Differentiating Anemia.—In addition to the exact measurements of the red cells which may be of importance in differentiating primary and secondary anemias, another

method has been suggested by A. V. St. George and A. Lincoln Brown (*Arch. Int. Med.*, 1925, **36**, 847) in which the information derived from a study of the icterus index is used as a basis for adding additional data to the study of a case in which differential diagnosis must be considered between primary and secondary anemia. These authors record a considerable series of cases in which they made careful studies of the blood findings with particular reference to the icterus index and they show quite definitely that the icterus index is a distinct clinical aid in separating the several types of anemias when these anemias are uncomplicated by cardiac insufficiency, biliary sepsis and pneumonia.

Efficiency of the Heart and Its Measurement.—This is the first of two lectures delivered by Dr. Yandell Henderson (*The Lancet*, 1925, **2**, 1265) at the University of London. Although this lecture was delivered primarily as a lecture in physiology, nevertheless it will repay reading by those in clinical medicine interested in cardiac physiology and the physiology of the circulation; subjects, incidentally, which should appeal to all internists and subjects in which a great deal of research work is now being conducted in this country as well as in other countries. Henderson's paper does not lend itself well to abstracting, but the conclusions that he draws from his studies are so interesting that they are well worth quoting in entirety. "The only adequate expression of the efficiency of the heart is one based on accurate measurement of the volume of blood that the heart pumps and upon the amount of oxygen consumed by the body. The relation between these two functions determines the arteriovenous oxygen difference, and thus determines the amount, and particularly the pressure of the oxygen supply to the working tissues of the body. In vigorous mammals of all sizes the arteriovenous oxygen difference during bodily rest is about 3 or 4 volumes per cent. The volume of the circulation in vigorous men and animals at rest is about 3 to 4 litres of blood per minute per square meter of skin surface. The stroke volume for animals and men of corresponding activity is a function of their body-weights not their surfaces. For all vigorous mammals, including man, the stroke index during rest is about 1.4 to 1.8 c.cm. per kilo per beat. The pulse-rate is in general proportional to the surface weight ratio and is thus in general an index of the intensity of respiratory metabolism. The mechanical conditions of the heart's activity and its own behavior make the right ventricle the meter of the circulation. The size of the stroke of this meter depends on the volume and pressure of the venous return. The veno-pressure mechanism is adjusted to act in relation to the intensity of the gaseous exchange of the tissues."

The Concentration of the Blood and the Urine in Diabetic Toxemia.—Harold A. Bulger and John P. Peters (*Arch. Int. Med.*, 1925, **36**, 857) find, in severe diabetic toxemia with marked dehydration of the blood, that the urinary chloride and nitrogen concentration is very low. Similarly the glucose content of the urine may drop as the dehydration comes on, even with a rising blood sugar concentration. There appears to be no direct relationship between the degree of dehydration and urinary changes, nor does the degree of hyperglycemia or glycosuria

seem to have any significance in these changes. The authors suggest that the kidney changes are not a result of the blood changes, but are probably brought on by the same toxic materials (ketone bodies?) acting independently on the kidneys. With insulin treatment, accompanied by glucose and saline administration, there is a rapid dilution of the blood and a rapid increase of nitrogen and chloride in the urine. They advise the giving of large amounts of glucose along with the insulin in these cases, to combat the toxic protein destruction, especially in cases with infection. Glycosuria and hyperglycosuria in themselves can be disregarded in this effort to quickly reduce the ketosis and acidosis.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Osteitis Fibrosa and the Hyperostotic Form of Bone Syphilis.—WILHELM (*Surg., Gynec. and Obst.*, 1925, **41**, 624) claims that there are gross anatomic and clinical resemblances between the hyperostotic form of syphilis of the long bones and osteitis fibrosa, both the senile hyperostotic-porotic form (Paget's disease) and the juvenile endosteal type. Coarser gross morphologic similarities, such as deformities, elongation and bowing, and especially the saber-blade form of tibia, are found in the affected bones of both diseases. Despite these external similarities, we are dealing, especially in regard to their histogenesis, with two fundamentally different diseases. The essential differences in their nature express themselves in the individual anatomicopathologic characteristics of the affected bones and also in their Roentgen pictures. Characteristic of hyperostotic syphilis are the marked, often tremendous participation of the periosteum, the more or less advanced narrowing and obliteration of the marrow cavity, the sclerotic or finely porous quality of the newly built bone tissue. The saber-blade, or saber-sheath, form of tibia in syphilis may be due purely to a periosteal new formation of bone or to an osteitic rebuilding and elongation resulting in a true bowing. Characteristic of the senile form of osteitis fibrosa are the absence of periosteal participation, the very great widening of the marrow cavity, even into the epiphyses, the frequent lengthwise splitting up of the compacta into lamellæ. The saber-blade tibia of Paget's disease is the result of rebuilding and elongation of the bone. In the juvenile endosteal hyperostotic-porotic form there is also a complete absence of periosteal involvement. The occurrence of more or less well-formed cysts or of single circumscribed dense foci accompanying a diffusely-spreading osteitic new-bone formation are disgnostic points in favor of osteitis fibrosa as against lues.

Malignant Tumors of the Kidney.—Hinman and Kutzman (*Calif. and West. Med.*, 1925, **23**, 429) say that the pathogenesis of kidney tumors is still in the hypothetical stage. The types most commonly found are the hypernephroma, occurring chiefly in late adult life, and embryonic mixed tumors, found in early childhood. Clinically, all renal tumors should be considered malignant, because of the great rarity of the benign type. The classic signs of kidney tumors are hematuria, pain and tumor. Hematuria is the most frequent initial symptom in adults, while tumor is in children. The importance of each symptom should be considered initially as it appears, and the diagnosis not allowed to wait until the clinical picture is complete. Only by thorough early investigation can we hope to influence the present appalling morbidity. The urologic examination should be complete, and include a differential examination of the urine functional studies and ureteropyelography.

Experimental Hydronephrosis.—Hinman and Hepler (*Arch. Surg.*, 1925, **2**, 649) claim that it is possible to reduce urinary secretion by a properly placed, partially obstructing rubber tube on the renal artery. When this procedure, which reduces the bloodflow and the intrarenal blood pressure, is combined with total ligation of the ureter on the same side hydronephrosis develops to a much greater degree and more rapidly than when the ureter alone is ligated. This increase in the rate of development of hydronephrotic atrophy in the presence of a reduced secretory pressure and oliguria indicates that back pressure and pressure atrophy have not quite the importance generally given, but that another factor is an equally or more determining one. This other factor is a nutritional one. The more rapid parenchymal degeneration, that results from the anemia of arterial compression, weakens resistance and accelerates dilatation in spite of the diminution in back pressure.

Hepatic Function in Health and Disease.—C. H. Mayo (*Surg., Gynec. and Obstet.*, 1926, **42**, 9) claims that the most common cause of death following surgical operations is disease of the lungs, the next renal complications and the third cardiac complications, although the latter condition is most feared by those who are ill. When the liver is under continued stress from congestion and the higher pressure from spasm of the sphincter of Oddi, it continues to form bile on account of the low blood pressure in liver tissue; the back pressure is not so serious nor so rapid in its results as chronic obstruction of the urinary bladder by a hypertrophied prostate. In certain cases when the liver is not functioning adequately, it may be relieved or assisted. Administering bile frees the gall bladder under tension during fasting. Its flow is increased by ox-gall and nitrogenous food, but not by calomel. Rich carbohydrate food checks it. In chronic deficiency of the liver associated with cirrhosis and splenic enlargement, the removal of the greatly enlarged spleen, reduces by 20 per cent the work of the liver and relieves and conserves the organ. In the probable deficiency consequent to chronic disease with emaciation, the lack of liver glycogen must be made up by intravenous injection of glucose.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

Exanthema Subitum.—VON BOKAY (*Deutsch. med. Wchnschr.*, 1925, **51**, 1687) reports the clinical findings in 11 cases of an acute illness of childhood that has been described under the name Exanthema Subitum in the American literature by Veeder and Hempelmann, Westcott, Levy and others. The disease has an acute onset, is characterized by no symptoms other than slight malaise and a fever that ranges from 102° to 104°, and after a duration of three, usually four, and occasionally five days, drops to normal by crisis. However, Glanzmann has observed a slight coryza with thin, watery nasal discharge and Levey has observed convulsions at the onset of the fever. During defervescence the rash appears; it is morbilliform, with spots ranging from 1.5 to 5 mm. in diameter, blanches on pressure, but promptly returns when the pressure is stopped. The rash appears first on the trunk where it is most abundant but rarely confluent, and may also involve the extremities and, to a less degree, the face. The rash reaches its height in twelve hours, and disappears completely in twenty-four to forty-eight hours. Desquamation has not been observed. There is a characteristic blood picture: Pronounced leukopenia (as low as 3200) with 80 to 90 per cent lymphocytes. Nine of von Bokay's cases were in infants under one year, and the oldest was two years old, but Veeder and Hempelmann met the condition in a boy of ten. The disease is apparently only very mildly contagious, having only once been observed in 2 children in the same household (Greenthal). The clinical course sharply differentiates the disease from measles and rubeola. The etiology is unknown.

The Comparative Sugar Content of the Blood and the Cerebrospinal Fluid in Various Conditions.—LEVINSON (*Am. J. Dis. Child.*, 1925, **30**, 774) found that the cerebrospinal fluid sugar in his series of nonmeningitic fluids varied between 46 and 76 mg. per 100 cc. of fluid. The lowest figure was obtained in a case of brain abscess, with a turbid fluid containing many leukocytes. The next lowest figure was 50 mg. per 100 cc. The cerebrospinal fluid sugar varied from day to day, and it bore no relation to the blood sugar. The cerebrospinal fluid sugar in all forms of meningitis was low, varying from 45 mg. per 100 cc. to a mere trace. In 1 case of meningococcus meningitis, the spinal fluid sugar was unusually high a few hours after onset, but it came down to 25 mg. per 100 cc. in less than twenty-four hours. The blood sugar in these cases of meningitis varied between 84 and 176 mg. per 100 cc. The sugar in the cerebrospinal fluid in a case of encephalitis showed an insignificant rise one hour after the injection of glucose, and a rise of 8 mg. three hours after the injection of glucose. Another time it showed an increase of 4 mg. in ten and a half hours. There was a rise of from

4 to 7 mg. in the cerebrospinal fluid sugar in a case of tuberculous meningitis one hour after the injection of glucose. In 1 case there was a marked rise in the cerebrospinal sugar two and a half hours after injection to 34 mg. In another case the cerebrospinal fluid sugar was practically at the preinjection level. The same was true three hours after the injection of glucose. Whenever possible the sugar in the cerebrospinal fluid should be determined on a specimen obtained several hours before the ingestion of food to exclude the possibility of error due to carbohydrate ingestion. For clinical purposes, there is no special advantage of determining blood sugar along with the cerebrospinal fluid sugar.

Nutritional Keratomalacia: Report of a Case.—SCHWARTZ (*J. Am. Med. Assn.*, 1925, **85**, 2025) reports a case that presents a number of unusual features. The appearance of keratomalacia three weeks after the apparent deprivation of fat soluble A constitutes a startingly rapid development of the disease. While in animal experimentation such rapid development often obtains, in such instances there is a different life cycle. It might be assumed that some comparative diet deficiency during the time preceding the actual onset of the symptoms, but in this case the infant was said to have been in perfect health prior to the onset of the illness. The study of the clinical history reveals in this instance a rather unusual manifestation of nervous symptoms. The first impression on examination of this patient was the presence of disease of the nervous system. In the differential diagnosis there were considered erythredemia, typhoid fever, tuberculous meningitis, scurvy and encephalitis. There was a very definite suggestion of cerebral irritation. In a study of the literature this appearance of nervous symptoms was not infrequently noted. The outstanding symptoms in this patient were stupor, irritability on being disturbed, weight loss and other evidences of nutritional disturbance as pallor and doughy skin, dry, inflamed mouth and cracked lips, fever and the characteristic corneal ulceration. The liver seemed unusually large and firm when the child was first seen. The symptoms suggestive of meningeal disturbance persisted for a number of days. Besides the symptoms in the case report, transient strabismus was noted the day prior to admission to the hospital. Spinal fluid examination showed no pleocytosis nor increased globulin. There was slightly diminished sugar reduction. The child lay in the froglike position occasionally observed in scurvy. As the child had had intergluteal hypodermic medication, it was difficult to rule out this factor in the position assumed. The patient showed complete recovery except for the loss of vision in the right eye. The response to the treatment with the fat soluble A substance in this case of keratomalacia was not nearly so striking as that often witnessed in scurvy following the use of orange juice. Despite the hypodermic injection of cod liver oil the convalescence was slow. The absorption of the cod liver oil given in this manner was very slow. It was three weeks after the specific treatment was begun before the weight curve and the other symptoms showed appreciable change. It seems obvious that the appearance of the characteristic eye changes are ominous of more nutritional changes than is apparent.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY AT THE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

CLEVELAND J. WHITE, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA.

The Etiology of Lupus Erythematosus.—A. M. H. GRAY (*British J. Dermat. and Syph.*, 1925, **37**, 406) believes: (1) That lupus erythematosus is a definite clinical entity and that it probably has a specific etiology, and (2) that the individual lesions are due to the local activity of microörganisms. Before attempting to state these assumptions, he surveys the prevailing opinions in a careful manner. As to the toxic theory, he cannot reconcile the clinical progress, especially the stage of atrophy, with any known purely toxic hypothesis; indeed there is no other condition of a slowly spreading non-ulcerative destructive inflammation of the skin which is not due to the activity of microörganisms in the affected tissues. As to the theory that certain specific organisms are at work in this disease, he first considers the tubercle bacillus. The tubercle bacillus has never been demonstrated in stained sections; guinea-pig inoculations from typical lesions have been consistently negative save on very rare occasions; the histology does not in the least suggest a tuberculous picture. The type of lesion is almost inconceivable for a tuberculid, the latter never being a progressive one in the sense that lupus erythematosus is. Tuberculosis is, however, a common accompaniment of the disease: It is possible that the disease either predisposes to tuberculous infection or lights up preëxisting tuberculous infection, or that tuberculous subjects are specially likely to contract lupus erythematosus. A more recent view has been put forward that the disease is due to the activity of the streptococci in the tooth-sockets, tonsils, nasal sinuses, intestinal tract, etc. It is, however, well recognized that streptococcal infection is a terminal manifestation in many acute conditions, and it is chiefly in the acute cases that streptococcus has been demonstrated. It is generally admitted that the streptococcus is practically a normal inhabitant of all mucous membranes. Local reactions to vaccines can scarcely be relied upon as a proof of streptococcal origin. In a few picked cases, the removal of the supposed source of infection has cured the condition, at least for the time being. The foregoing discussion is essentially theoretical and based on reasoning by analogy rather than proof.

Dermatitis in Association with Disease or Injury of the Peripheral Nerves.—BECKER (*Arch. Dermat. and Syph.*, 1925, **12**, 235) reports a case of persistent eczema on the right side of the face of a women, aged forty-seven years; the condition appearing three weeks after the pos-

terior root of the right trigeminal nerve had been sectioned for relief of trigeminal neuralgia. When first observed (eight months after onset), neurologic examination revealed complete anesthesia of the right side of the face and scalp, including the oral mucosæ. Twenty months later there was essentially no change in the dermatologic picture. Local applications had merely kept the skin smooth. Neurologically, motor control had been regained but marked caries and pyorrhea were present, affecting only the right side of the mouth. A critical review of the literature had revealed no case similar to the one reported; mention is made of 5 cases of transient mild cutaneous changes with no detailed neurologic findings given. As to the etiology, the author concludes that experimental and clinical observations would seem to indicate that toxic, infectious or mechanical irritation of the sensory nerves can be instrumental in producing this type of lesion.

Dermatosis Industrialis in Blue-print Workers Due to Chromium Compounds.—Parkhurst (*Arch. Dermat. and Syph.*, 1925, **12**, 253) concludes after observing 3 cases that erythematovesicular and small papular dermatitis may follow contact of potassium bichromate with the skin in susceptible persons, and that this dermatitis may be avoided by frequently rinsing the exposed skin with a saturated solution of sodium bisulphite and then with water, or by wearing properly fitting, intact rubber gloves.

Experimental Studies on Immunity in Herpes Simplex, with Notes on the Infectivity of the Blood and Spinal Fluid and on the Filtrability of the Herpetic Virus.—In a series of well-controlled experiments, S. S. Greenbaum and M. J. Harkins (*Arch. Dermat. and Syph.*, 1925, **11**, 789) found that herpetic disease in rabbits is a generalized infection; that mild herpetic virus infections do not protect against severe herpetic virus infections; and that complement-fixing substances do not develop in herpetic disease.

OBSTETRICS

NORRIS W. VAUX, M.D.,

CLINICAL PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

An Obstetric Retrospect.—Bjornson (*Canadian Med. Assn. J.*, 1925, **15**, 1236) asks the question, "Have obstetrics kept pace with the other branches of the healing art, and has its progress been as rapid and striking as that of surgery and medicine?" Regarding the manner and mode of the practice of surgery and obstetrics, in the former the major operation is seldom heard of being carried out in any place but a well-equipped hospital, yet obstetric practice in the major part takes place in the all but clean, aseptic or antiseptic homes. Surgical technic has taken longer to establish in the home than in a well-equipped institution. Today it is hard to find a gloveless surgeon, yet we would not

have to seek far for the gloveless obstetrician. Midwifery is done in all possible surroundings, and with surgical technic carried out well has met with good results even in complicated cases. How do end results of midwifery today compare with those of twenty-five years ago? In the quarter century past there have been many changes in obstetrics, some have brought improvement, while others have not met with success. There are some who hold to the conservative technic and methods and assume an attitude of noninterference through pregnancy and labor. With these the radical methods often conflict. The radicalists base their methods on the fact that pregnancy is a disease of nine months' duration. That every labor is abnormal and should be treated as a surgical procedure. All manner of methods are necessarily used in the combination, from the watchful waiting procedure to the injection of pituitrin, episiotomy, version, application of forceps and Cesarean section. The most frequent and pernicious error in obstetrics is the routine use of pituitrin, which must be condemned. Equally to be condemned is the routine performance of episiotomy regardless of whether the perineum offers an obstacle to delivery or not. So also is condemned the untimely and injudicious use of forceps and the fast-spreading fad of delivery by podalic version. All of the above-mentioned procedures may be of greatest benefit and legitimate when timely and skilfully used in hands trained and become expert in the performance and practice of these difficult operations. The end results of the radical versus the conservative in the last twenty-five years is as yet a draw, yet the greatest benefit has been accomplished in the outstanding advancement and marked betterment of the obstetric practice in general. In the obstetrical improvement the prenatal care stands alone, and needs no further proof other than the fact that the once common fatal toxemias of pregnancy in early or late gestation are now met but rarely. If careful instruction and supervision are given the expectant mother, the insidious onset of any abnormality of pregnancy is not allowed to reach a stage where the patient's life is threatened; contracted pelvis, placenta previa, fetal abnormalities and many other complications and diseases are treated and adjusted before the patient is called upon to pass into labor, with at times impossible delivery, with some serious outcome for her offspring and bad prognosis for herself. The author closes with the statement that "we have reason to congratulate ourselves that we are living in an age of newer and better obstetrics, where we can reap the benefits of the experience of eminent teachers of great ability and scientific training, whose life work has been devoted to raising the science of obstetrics from its former lowly state and placing it on a safe and sane scientific basis."

Treatment of Sepsis with Mercurochrome-220 Soluble.—St. George (*J. Am. Med. Assn.*, 1925, **85**, 2005) in reporting 5 fatal cases upon which the necropsy findings are elaborated, calls attention to the accumulation of the literature extolling the virtue of this antiseptic administered intravenously, and refers to the meager articles reporting unfavorable symptoms following the administration of the preparation. The author sends out a word advising more caution and control in its application. It is in the case reports here presented that the opinion is given that mercurochrome induced the intense nephritic and intestinal

lesions and this contributed death. Clinical analysis of the viscera by a competent chemist and toxicologist showed mercury in even larger amounts than were found in cases of mercuro-chlorid poisoning, indicating the marked toxicity of this drug and justifying the opening statement. It is further stated that cases have been reported where the drug was used successfully although a temporary nephritis and colitis accompanied its use. In cases of mercuro-chlorid poisoning where the kidneys and colon were severely involved and where recovery took place a subsequent chronic nephritis was present, a factor which has not yet been determined in mercurochromic cases.

The Value of Roentgen Ray in Obstetrics.—Ross, Mitchell and MacCharles (*Canadian Med. Assn. J.*, 1925, **15**, 1202). The article deals with all phases of Roentgen ray work in obstetrics, and is divided into four periods relative to the pregnancy. Before pregnancy the Roentgen rays are used to throw light on the size, shape and general conformation of the pelvis, the effect on the development of the pelvis of such lesion as congenital dislocation of the hip, tuberculous coxitis, fractures of the pelvis, bony tumors, sacro-iliac disease, exostosis, etc. In the first trimester of pregnancy the authors have utilized the Roentgen ray chiefly for the study of the pelvis. Attention is called to the work of Reuben Peterson, who believes that the definite enlargement of the uterine isthmus can be demonstrated by means of pneumoperitoneal roentgenography from the sixth to the tenth week of pregnancy and is, he believes, a definite sign of intrauterine pregnancy. A satisfactory result can be obtained of the fetal skeleton from four to four and a half months of pregnancy. Early pictures may show, under favorable conditions, at least a part of the fetal skeleton. In the second trimester a satisfactory Roentgen ray result of fetal skeleton can be usually obtained. The occipital bone is in the majority of cases more clearly outlined by its density when the head is seen; when the other cranial bones are visible the occiput is always the most dense structure. The article mentions the work of Lynch, whose study of the pelvis concluded that in many women there is a considerable separation at the symphysis and the sacro-iliac joints during pregnancy and labor. In the third trimester the entire fetal skeleton can be demonstrated except in very obese subjects. The position in utero and the presenting part are easily determined. Patients Roentgen rayed at subsequent dates showed variation of positions. The comparative proportion of the fetal head and the pelvic inlet can also be determined. The diagnosis of twins and triplets is verified. Where pregnancy is denied, especially if illegitimacy is suspected, the unmistakable shadow of a fetal skeleton will convince the self-deluded victim of pseudocyesis that no pregnancy exists. Fetal abnormalities, a hydrocephalus, spina bifida, double monsters can be diagnosed before delivery. The possible association of placenta previa with abnormalities and if possible the advisability of ascertaining by Roentgen ray whether the fetus has a deformity. The possibility of diagnosing definitely the death of the fetus in utero by the overlapping of the skull bones with distant signs of shrinkage of the skull contents can be readily detected. After labor separation of pelvic joints and fractures of the maternal pelvis are easily demonstrated, as well as fracture of the skull and long bones of the child.

Dextrocardia and other abnormalities can likewise be detected. The technic in radiography of pregnancy is easily carried out by one familiar with radiographic work and consists of the following: The patient is placed in a prone position with chest and thighs supported with pillows; the factors used are 10 M.A. current, 87 K.V., 15 seconds' exposure.

GYNECOLOGY

UNDER THE CHARGE OF
JOHN G. CLARK, M.D.,
PROFESSOR OF GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,
AND
FRANK B. BLOCK, M.D.,
INSTRUCTOR IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

New Method of Repair of Injured Ureter.—In the experience of most gynecologists there will come a time when a convenient and safe method for the repair of a damaged ureter will be of great value, and the method which has been suggested by McArthur (*Surg., Gynec. and Obstet.*, 1925, **41**, 719) may be of value. According to his technic, given a missing portion of a ureter, even 1 to 2 inches in length, a longitudinal slit is made in the side of the *proximal* portion sufficiently long to admit two catheters. One of these, a rubber urethral catheter, is inserted upward to the renal pelvis; the second, a *ureteral* catheter of good size, is inserted downward so that it passes out of the proximal end, and bridges the gap to the proximal end of the distal remaining ureter. Both ends of the ureter are then approximated as closely as feasible by absorbable stitches. The catheters are then brought to the surface and permanently secured to the skin by stitches or other devices. All the urine from that kidney is thus diverted from the field of operation during the time of epithelization. The body tissues heal together around the catheter, bridging the gap between the renal end and vesical end, and the catheter simply remains *in situ* until in the judgment of the operator an epithelial lining has had time to grow between the ends. No experimental work along these lines has determined the *time* element; but that epithelization does occur has been amply demonstrated in the various reconstruction methods that have proved successful. Whether the missing portion of the ureter is lacking by accident or design (as because of malignant disease), when the ureter is too short to be implanted in the bladder, the above technic can be applied with safety and success.

Carcinoma of the Fundus.—A series of 269 cases of carcinoma of the fundus in which hysterectomy was performed at the Mayo Clinic between 1907 and 1921, and also 41 cases treated by radium between 1916 and 1921 have been reported by Stacy (*Radiology*, 1925, **5**, 331). In this series 64 per cent had passed the menopause an average of nine years. The average age of the patients still menstruating was forty-

seven years. Of the patients who had a hysterectomy performed after the menopause the first symptom noted was metrorrhagia in 61 per cent, foul discharge in 19 per cent, watery discharge in 14 per cent, and a definite hemorrhage in 2 per cent. There was pelvic pain in only 4 patients. Of those still menstruating the first symptom was metrorrhagia in 52 per cent, irregular menstruation in 8 per cent, hemorrhage in 4 per cent, profuse menstruation in 2 per cent and bloody, foul or watery discharge in 28 per cent. Of 269 cases operated upon, 215 had a total abdominal hysterectomy and 54 had a vaginal hysterectomy with a primary mortality of 5.2 per cent. Of 215 cases traced, 50.2 per cent were living more than four years and 49.8 per cent were dead. Stacy believes that the prognosis of cancer depends upon the age of the patient, the grade of malignancy and the personal resistance to cancer. Of the 32 radium cases traced, 31 per cent lived more than three years, 18 per cent more than five years. She concludes that in the early cases of carcinoma of the fundus surgical treatment is better than radium, but irradiation is indicated in those patients presenting definite contraindications to surgery because of some general condition or extensive malignancy and in the control of vaginal recurrences. While total abdominal hysterectomy is attended by higher operative mortality there is a higher per cent of four-year cures.

Ovarian Grafting.—We do not hear much in this country about the subject of ovarian grafting, possibly because the feeling of many gynecologists may be that it is not worth the trouble or it may be that the technic has not been properly followed and, therefore, the results have been poor. Much work has been done, however, in this field by certain foreign gynecologists, among whom BELL (*Surg., Gynec. and Obstet.*, 1925, **41**, 706) of Liverpool is a well-known enthusiast. He is very particular to state that he performs ovarian grafting only when it is impossible to leave an ovary or part of an ovary in the normal site during the reproductive period. Such an eventuality is, however, produced by gonorrheal infection. It should not for a moment be imagined that because the case is one of salpingitis the ovaries must be transplanted; this is far from being the case. Often it is possible for the surgeon to cut through the mesosalpinx and to remove a diseased tube without injuring the ovarian blood supply. When, however, there is a large pyosalpinx the two layers of the mesosalpinx may be widely separated, and any attempt to excise the tube alone leads to interference with the ovarian vessels. It is this that causes the ovary, if it be retained in the pelvis, to undergo "cystic degeneration." The ovarian tissue removed is separated from other structures, such as the tube, and a long silk thread on a sharp needle is passed through it. The two ends of the thread are knotted together, and the ovary so tethered is placed in the pouch of Douglas, or elsewhere in the peritoneal cavity, the ends of the thread being brought through the laparotomy opening and held in a pair of forceps. In this way the ovarian tissue is kept moist and warm in natural surroundings until required for grafting. When the operation for the primary lesion has been completed, but before the laparotomy wound is closed, the ovary is recovered by withdrawing the thread attached to it, and is placed on a small square of rubber 6 inches in diameter, and about $\frac{1}{4}$ inch in thickness, which has been sterilized in

readiness. A very sharp grafting knife is taken, and the hard cortex is shaved off the ovary or pieces of ovary, as the case may be. Then, by a series of crisscross incisions, the whole piece of ovary is divided into small parts which are still held together by the underlying tissue. It is merely for convenience in handling that the ovary is not cut into separate fragments. The exposure of such a large area of surface and the limited size of the fragments tend to ensure rapid vascularization of the implanted tissue. There is also less chance of follicular cyst formation. Next, the aponeurosis covering the rectus on one side of the laparotomy incision is seized with a pair of compression forceps and drawn towards the operator, who with a knife carefully makes a small incision through the upper surface, avoiding all vessels. The blunt point made by the closed blades of a long angular compression forceps is passed through the opening in the rectus sheath and gently forced into the body of the rectus muscle *parallel to the surface*. The blades are then slowly separated. It is most important that there be no bleeding, for, although grafts must be implanted in vascular areas, if the grafted tissue is bathed in blood it cannot become attached to the surrounding structures from which nutriment is to be drawn. The ovarian graft is now passed into the middle of the muscle and laid flat among the fibers. The edges of the opening in the rectus sheath are brought together with a couple of sutures, and the laparotomy wound is closed. It appears that by the method practised functional results may be expected in a little over 80 per cent of all cases. By "functional results" he means that the symptoms of the menopause are abolished, at any rate after the first few months following operation, and do not reappear for some years. It will be noted also that in those patients in whom a portion at least of the uterus was conserved—usually by the Bell-Beuttner procedure—menstruation reappeared in no less than 66 per cent.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,

MERCY HOSPITAL, PITTSBURGH, PA.

A Clinical Study of Bone Conduction after the Method of Runge.—"Most otologists believe that there is a standard, or normal, bone conduction; that is to say, that any certain tuning fork should be heard when its stem is pressed against any part of the head for a length of time, which, for clinical purposes, is constant enough to make it possible to fix a standard for any particular fork that, within reasonable limits, will not vary greatly in any number of normal persons. On this assumption, many tests of hearing by bone conduction have become established, several of which have been universally accepted and used for years in all routine examinations of the ear. It has never been definitely determined, however, whether hearing by bone conduction is, as taught by

Bezold, simply the perception of those sound waves which, on their way to the labyrinth, have passed through the sound conduction apparatus; or whether, as argued by Wittmaack and others, there is a direct cranio-labyrinthine transmission of the sonorous vibrations. The question is an important one, for, under the Bezold theory, all sound waves which reach the labyrinth directly, that is, without appropriate intervention of the sound conduction mechanism, are inaudible; consequently our hearing tests by bone conduction are simply additional methods of diagnosis in lesions of the conduction apparatus and only of suggestive value in determining the presence of perception deafness. On the other hand, if there is, at least in part, a direct craniolabyrinthine transmission, our bone conduction tests take on an added significance, and hearing by bone conduction can be considered as a phenomenon separate and distinct from physiologic air conduction and of greater value in differential diagnosis." In 1923, Runge described his "water-filling" test. The test is made, first, by taking the patient's bone conduction with the fork on the mastoid; the head is then placed over to one side, the ear filled with 1 cc of water and the bone conduction again taken. Runge found in the normal ear that "water-filling" about doubled the duration of perception by bone conduction up to C^2 fork (512 d.v.); above this pitch the reaction was not so pronounced. He further found that in pathological cases the results were entirely different. For instance, after the radical mastoid operation, "water-filling" did not increase the bone conduction; if there was evidence of complete fixation of the stapes, the test did not increase the bone conduction; if there was only partial ankylosis somewhere in the ossicular chain, the "water-filling" gave only a moderate increase in the duration of bone conduction; if there was evidence of cochlear degeneration, bone conduction which was greatly reduced could usually be somewhat increased by "water-filling;" and in acute otitis media bone conduction could be slightly diminished or at least not increased by the test. In a series of more than 50 patients suffering from a variety of otological conditions, Downey (*Arch. Otolaryngol.*, 1925, **2**, 260) obtained results which corresponded almost exactly with those quoted from Runge. From a practical standpoint the test appeared of especial valuable diagnostic significance in those conditions for which there seems to be no better term than the chief symptom, chronic progressive deafness. Failure to increase bone conduction by the Runge test occurred most frequently in those patients in whom increased bone conduction already existed, and who presented other signs of stapedial fixation or of profound disturbances of the conduction mechanism. In these patients one could not expect treatment to be of benefit. On the other hand, if bone conduction could be increased some gain in hearing was usually obtained. After several interesting and instructive case reports and a detailed discussion of the various theories of hearing as they relate to the interpretations of the test, the author concludes that many problems of deranged hearing can be solved only by the physicist interested in otology and the otologist interested in physics working together, for otherwise the physicist sees only the normal, and the otologist, as Gradinego has well expressed it, "sees only a deformed likeness of hearing." As a clinical otologist, the author feels that hearing by bone conduction may, for diagnostic purposes at least, be considered a distinct entity, but stands ready to be otherwise convinced.

Quantitative Experimental Evidence on the Acuity for Hearing by Bone Transmission.—POHLMAN and KRANZ (*Proc. Soc. Exper. Biol. and Med.*, 1925, **23**, 76) submit some "very general conclusions based on the observations made on individuals with known sensitivity for air-transmitted sound." A continuous tone scale was employed by an apparatus previously described and the threshold approached from below as in the air tests. Sensitivity for bone transmission of sound varies a great deal more than that for air-transmitted sound, and is not definitely related to it. The sensitivity at any given frequency is not a criterion of the sensitivities at other pitches (about 500 v.p.s being the least variable). Areas of marked decrease in air acuity are similarly registered through the bone. In normal ears the hearing is most acute at normal pressure for both air and bone transmitted sound, the development of plus and minus pressures in the air of the external auditory canal decreases acuity for both series of tests, and leads to the conclusion that the cranio-tympanic conception of sound transmission is probably the correct one. In comparing the acuity for bone-transmitted sound, with the external meati open, as opposed to the external meati occluded, it was found that the individual with the greatest sensitivity through the bone with the ears open showed the least advantage on closing the external canals. It was also observed that the enhancement in bone transmission due to occlusion of the canals became less pronounced as the pitch rose and was most marked in the low part of the tone scale.

"Areas of Lowered Acuity" in Relation to Quantitative Tests on Bone and Air-transmitted Sound.—"Adult individuals often show an area of decreased acuity for air transmitted sounds in the range between 2400 and 3000 pps. in the auditory field of frequency. Such ranges of decreased acuity are often sharply defined and may require a stimulus up to 500 or 1000 times the normal minimum to elicit response. This finding might be explained by almost any of the numerous theories of end-organ behavior on the basis of a local defect in the basilar or tectorial membranes." In an investigation along these lines, POHLMAN and FRANZ (*Proc. Soc. Exper. Biol. and Med.*, 1925, **23**, 138) observed that one individual, who had had a constant bilateral defect in this frequency range for at least four years, also showed a decreased bone acuity through the same range of frequency. A second subject, with a unilateral defect in air acuity for at least five years also exhibited a defect in bone acuity when tested with the bone activating telephone. The third person displayed no lowered air acuity through this range but did show a decreased bone acuity similar to the two previous cases. Four more people with normal air acuity did not show the bone acuity defect. Control observations were made with a different instrument. The authors feel that the report "is of peculiar significance because the defect which might have been interpreted in terms of internal ear reaction if occurring in both bone and air acuity, cannot be so interpreted because it can occur in the bone acuity without being present in the air acuity." While they are unable to offer an explanation of the phenomena they believe that "the demonstration of this effect in the sound trasmission apparatus is a serious obstacle to the differential diagnosis between a conduction and a perception deafness."

RADIOLOGY

UNDER THE CHARGE OF

RUSSELL D. CARMAN, M.D.,

HEAD OF THE SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

AND

CHARLES G. SUTHERLAND, M.B.,

ASSOCIATE IN SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

The Effect of Roentgen Rays on Callus Formation in Ununited Fractures.—The effect of Roentgen rays on bone, according to POHLE (*Radiology*, 1925, **5**, 67), is the same as on other tissues, and that there are stimulating as well as destructive doses. Observations on the human skeleton and on animals have shown a very marked influence of Roentgen rays on the healing of fractures when irradiated one to ten days after fracture. In cases of poor callus formation one or more exposures to Roentgen rays will lead to healing of the fracture. The author cites 15 cases of fracture with little or no callus, of which 11 were clinically healed, 3 did not respond and 1 is still under treatment. With this degree of success, he urges that this method be tried out more fully and cases reported in order that the true value of this method of treatment can be ascertained.

Differential Diagnosis of Gallstones and Kidney Stones.—Although gallstones and kidney stones when typical can often be easily differentiated one from the other, according to NICHOLS (*Radiology*, 1925, **5**, 107) there is a certain percentage of cases in which calculi cannot be so easily recognized by their size, shape or general appearance. He has found that the difference in size of the calculi when taken both from the anterior-posterior and posterior-anterior positions is a guide to their differentiation and especially in fat patients. For further differentiation pyelograms should be made in order to recognize more definitely or rule out a kidney stone. Also, the gallbladder should be studied with the gastrointestinal examination for direct or indirect evidence of gallbladder disease.

Diverticulum of the Stomach: Accidental Finding in Routine Examination.—GRAY (*Am. J. Roentgenol. and Radium Therap.*, 1925, **14**, 110) reports a case of diverticulum of the stomach which was free from symptoms. Roentgenoscopy showed a fingerlike projection near the cardia on the lesser curvature, which remained visible for seven days by retained barium. In the cardiac region the musculature is so arranged that the stomach wall is weakest here, and this probably accounts for the more frequent occurrence of diverticula in this portion. The author quotes Akerlund who has divided the diverticula of the stomach into two groups, the acquired and the congenital, saying that the former appear near the pylorus and the latter in the cardiac region. Diverticula appear most commonly in women. The author has shown by a search of the literature that diverticula are rather uncommon, that they have no symptom complex which is characteristic and that they are usually found only in routine examinations.

Roentgenographic Demonstration of Adenoids.—Grandy (*Am. J. Roentgenol. and Radium Therap.*, 1925, **14**, 114) reports the roentgenogram of a child's head in the lateral view which definitely showed the presence of adenoid tissue. This led him to further study, and he found that because of the anatomy of the nasopharynx it is comparatively easy to recognize adenoid tissue which stands out clearly, due, possibly, to the photographing against an air space which shows black. This method is a check on the operator in the removal of adenoids and demonstrates the fact that adenoid tissue may return after adenectomy.

Common Causes of Shoulder Pain.—Butler and Elward (*Am. J. Roentgenol. and Radium Therap.*, 1925, **13**, 536) give a review of the anatomy of the shoulder joint and adjacent structures. They also review the listed causes of shoulder pain as given in the *Index to Differential Diagnosis*, and in the works of Orr and others. These are very numerous and far-reaching. They call attention to the fact that hypertrophic changes of the lower four cervical vertebræ, calcified glands in the neck and spurs on the under surface of the clavicle may press on nerves and cause pain. Opaque subdeltoid or subcoracoid bursitis, which may or may not be due to calcium deposits, are diagnosed readily by the Roentgen ray. On the basis of referred impulses, in considering the origin of the phrenic nerve as arising from the fourth cervical and recurring branches from the third and fifth cervical, with distribution to the diaphragm, pericardium and pleura, it is readily seen how abdominal and chest conditions may give rise to referred pains in the shoulder. A 10 by 12 film can be so placed as to include in addition to the shoulder joint the lateral cervical region, the supraclavicular region and the portion of the thorax on the one side and the superior mediastinum. This makes it possible to demonstrate the presence of the following lesions when present: Caries, or erosion of the cervical vertebræ, cervical ribs, cervical arthritis, calcified cervical glands, spur on the clavicle, opaque subdeltoid bursa, aortic aneurysm, apical tuberculosis, apical neoplasm, mediastinal new growth, Hodgkin's disease and demonstrable lesions of the joint itself.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY AT UNIVERSITY OF COLORADO, DENVER, COLORADO.

AND

LLOYD H. ZIEGLER, M.D.,

ASSOCIATE IN PSYCHIATRY AT UNIVERSITY OF COLORADO, DENVER, COLORADO.

Encephalitis Lethargica—Its Psychological Implications.—Auden (*J. Ment. Sci.*, 1925, **71**, 647) quotes von Economo as to the psychiatric significance of this new disease in pointing the way to further researches

in the realm of structure and function. The author gives his experience with 64 children (postencephalitic cases) five to fifteen years of age, in whom he has noticed a great variety of behavior disorders which he tabulates as follows: Reduced intelligence in 30; disturbed sleep rhythm in 55; marked irritability in 49; character changes and moral defects in 21; Parkinsonism, tremors, bradykinesis, etc., in 30; perverted habits in 32. The disturbed sleep rhythm and irritability are reported as very annoying to the parents and associates of these patients. Many of these children preferred to sleep by day and were noisy and boisterous at night. Three brief case histories are given. The author likens the effects of encephalitis to alcohol in that inhibitions are removed and the protopathic elements (Head and Rivers) of the nervous system dominate, while the epicritic elements apparently fail to develop as they should. He strongly recommends the establishment of special institutions for the care of such unfortunate children.

Vasectomy and Its Influence Upon 100 Cases of Dementia Precox.—STERN, FOLSOM and RITTER (*State Hosp. Quart.*, 1925, **10**, 404) performed the vasectomies between March, 1923, and May, 1924. Of the group, 49 were hebephrenic type, 40 paranoid, 7 catatonic, and 4 simple. The effect of the vasectomies is as follows: 71 showed no mental or physical improvement; 17 showed no mental but slight physical improvement; 6 showed no physical change but slight mental improvement; 6 showed slight physical and mental improvement. In 78 there were no gross changes in the testes or prostate. Slight changes occurred in the others. No material was studied microscopically. The authors feel that vasectomy is of no value in dementia precox.

An Unusual Manifestation of Metastatic Miliary Carcinomatosis of the Central Nervous System.—LEWIS (*Am. J. Psychiat.*, 1925, **82**, 171) presents the case of a man, aged twenty-seven years, whose whole illness was not over two months. The onset was at night and characterized as "delirious" talk and severe abdominal pain. He worked after the onset, but fatigued easily and did not always seem to know what he was doing. He was early diagnosed as a catatonic dementia precox by experienced psychiatrists. When neurological signs developed, he was thought to have epidemic encephalitis. At autopsy no gross tumors were found in the organs. The brain was somewhat swollen in places. Microscopic examination of the brain revealed generalized miliary carcinomatosis. Although no cancer was found in the body, the author feels that the brain involvement was most likely secondary and he thinks it may have been from the lung.

New Method of Recording Muscular Tremors.—BEALL (*Arch. Neurol. and Psychiat.*, 1925, **14**, 751) divides tremors into three classes: Toxic, organic, and functional. He presents a new instrument for recording very accurately the horizontal and vertical components of a tremor. Numerous tremographs are given from a variety of patients. Tremors due to organic changes in the central nervous system are irregular in amplitude and rate. Those due to endogenous or exogenous toxins are rapid and regular in rate and contour. Psychoneurotic tremors are most like toxic tremors.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
OSKAR KLOTZ., M.D., C.M.,
PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,
AND
W. L. HOLMAN, M.D.,
ASSOCIATE PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Diphtheria Antitoxin.—A valuable series of communications by GLENNY and his collaborators (*Jour. Path. and Bacteriol.*, 1925, **28**, 241, etc.) contributes to the knowledge of diphtheria toxin and antitoxin. In *Diphtheria Antitoxin in the Blood of Normal Horses* (p. 241) he presents further evidence of the existence of natural antitoxin in the blood of horses, but states that the source has never been satisfactorily identified. These horses produce antitoxin rapidly, while those with no normal immunity do not respond as well. In 1350 horses tested on admission during seventeen years, about half contained 0.1 unit or more antitoxin per 1 cc. The percentage of horses possessing normal immunity has greatly decreased in recent years. This may be attributed to the supplanting of horses in the city streets by motor cars and the relegation of the former to country districts. Horses possessing normal immunity showed considerable fluctuation of antitoxic titer while under observation, though no injection of diphtheria toxin had been given. In the second article, *The Relation between Dosage and Death Time* (p. 251), he discusses a question of theoretical rather than practical interest. Lethal times were observed on guinea pigs injected with varying doses of strong diphtheria toxin and a closely applicable formula is reported. The minimum lethal time was found to be ten hours. Sex had no effect. Cobra venom was also examined, and a formula for it is given. Experimentally and mathematically the paper is interesting. Next, GLENNY and HOPKINS contribute the *Time of Combination of Diphtheria Toxin with Living Tissues* (p. 261). It was found that if a Schick dose of toxin be given intradermically neither 10,000 times its equivalent in antitoxin (10 units) injected intravenously fifteen minutes later, nor 1,000,000 times its equivalent in antitoxin (1000 units), given intravenously thirty minutes later, is sufficient to prevent the appearance of a small reaction. The size of the reaction produced by a Schick dose of toxin can be controlled by suitable injections of antitoxin within given time intervals and by the routes designated. The intravenous is the most rapid route, intramuscular the next and subcutaneous by far the slowest. A Schick dose of toxin given to an immune rabbit acts as a secondary stimulus, causing an increase in antitoxic titer of the blood, even although 1000 units of antitoxin be given intravenously three hours after injection of the toxin. The fourth paper is by GLENNY and POPE (p. 273) and deals with *The Antigenic Effect of Intravenous Injection of Diphtheria Toxin*. Working with rabbits it was found that the intravenous injection of diphtheria toxin-antitoxin mixture produces a

primary stimulus response. Partly neutralized modified toxin was more effective than unneutralized. It is also reported that the intravenous injection of diphtheria toxin can act as a secondary stimulus. The fifth of the series, *The Measurement of the Combining Power of Diphtheria Toxin and Toxoid with Antitoxin in Relation to Their Antigenic Efficacy* (p. 279), is from GLENNY, POPE and WADDINGTON. It has been their experience that some batches of toxin which have shown a low toxicity, judged by the M.L.D. or L+ (or L_0) dose, have proved to be of high immunizing efficiency. The question of measuring combining power is thoroughly discussed, and the authors occupy themselves with comparing the various animal tests for diphtheria toxin with one another, and contrasting them with the *in vitro* test in an endeavor to establish the best test of antigenic efficiency. It is shown that the various *in vivo* tests fail to indicate the correct binding capacity of toxin, and it is pointed out that the indicating mixture or mixture containing the "precipitate indicateur" consists of exact equivalents of toxin plus toxoid and antitoxin. It is concluded that antitoxin has a greater affinity for toxin than for toxoid; that toxin and antitoxin can dissociate from combination, the degree varying with different samples of antitoxin, and finally that both specific toxin and toxoid are antigenic. GLENNY, HOPKINS and WADDINGTON further report *The Effect of Serum Sensitiveness and Precipitin Formation upon the Efficacy of Diphtheria Toxoid and Toxin-antitoxin Mixtures in Promoting Antitoxin Production* (p. 305). It is shown that if a rabbit be sensitized with horse serum, and is later given an injection of horse serum, rapid precipitin formation follows; if an injection of diphtheria toxin-horse-antitoxin mixture be given during this stage of active precipitin formation, the mixture fails as a primary and a secondary stimulus. It is believed that this observed phenomenon is entirely due to a "crowding out" of cellular activity by precipitin formation, and it is shown in support of this view that: (*a*) Precipitin formation prevents the action of toxin-horse-antitoxin mixture even when the heterologous cow or goat serum precipitin is being formed; (*b*) the formation of precipitin to horse serum has a marked inhibitory action on the antigenic power of diphtheria toxoid. The seventh paper, by GLENNY and WALLACE, *The Titration of Diphtheria Toxin by the Flocculation Method* (p. 317), is a detailed report of the technic followed by them in carrying out the test, and is one which can be employed by assistants with but little previous training. A more accurate definition of an L_f dose of toxin is given; it is "The amount of toxin per unit of a certain chosen antitoxin in the mixture that flocculates more rapidly, under the same conditions, than all other mixtures containing other amounts of the same toxin per unit of the same antitoxin." The test is thoroughly discussed and described. Ninety per cent of the tests made in the manner indicated are correct to within 10 per cent, and a single worker can with ease prepare and read fifty series of tests in one day. The phenomenon of nonspecific flocculation is pointed out. The final paper of the series is entitled *Immunologic Notes* (p. 333), and is contributed by GLENNY, POPE, WADDINGTON and WALLACE, with acknowledgments to others. It consists of a series of interesting, though unconnected, completed experiments in connection with the mechanism of immunity. The first deals with

differences in response given by individual guinea pigs to the injection of an antigen. Then the variation in antigenic response according to the method of injection is discussed. Another experiment shows that young guinea pigs tend to be less readily immunized than older animals. Some work on the effect of the addition of small amounts of toxin on the antigenic value of modified toxin is given. This value was found to be considerably increased, and it is suggested that other toxic substances may act in the same way, one experiment indicating this, having been carried out with Bacillus welchii toxin. The antigenic value of modified toxin after boiling is reported on, followed by experiments on the antigenic value of the partly neutralized toxoid. Finally, it is shown that by the daily injection of very small amounts of toxin, in all less than 3 M.L.D., guinea pigs have been rendered immune (Schick negative) in twenty-two days. The whole series of papers is well arranged and is of undoubted value to the immunologist.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Tetanus from Vaccination Dressings.—The U. S. Public Health Service (*Pub. Health Rpts.*, 1925, **40**, 559) makes the following announcement: The United States Public Health Service issues a warning to the medical profession and to the public against the use of bunion pads as a dressing in vaccination against smallpox. This singular use of bunion pads appears to be more common than would be supposed. Several fatal cases of tetanus following their use have recently occurred in the United States, and laboratory tests have demonstrated the presence of tetanus spores in bunion pads from the same source as those which were associated with tetanus cases. The Public Health Service deprecates the use of any kind of a shield as a vaccination dressing. The employment of such a shield tends to prevent evaporation, to retain heat, moisture or discharges, with a consequent softening of the vesicle, to obstruct lymphatic drainage, to produce hyperemia and to create conditions apparently favorable for the development of bacterial invasion, especially by the tetanus organism. The smallest single site insertion compatible with a successful take and with no immediate dressing whatever is believed to be the best method of vaccination in the majority of cases. The *Public Health Reports* (1925, **40**, 1351) give the following summary of the data on which this warning was founded: "(1) Eleven cases of postvaccination tetanus are reported following the use of bunion pads as vaccination dressing. (2) Tetanus organisms were demonstrated in approximately 25 per cent of 200 pads of the same makes as those used

on cases developing tetanus. (3) The 11 cases in which tetanus developed were all vaccinated by the scarification method; in 9 the vaccination was primary, while in 2 the vaccination history is unknown."

Vaccination by Mouth Against Bacillary Dysentery—ENLOWS (*Pub. Health Rpts.*, 1925, **40**, 639) gives the following as summary and conclusions: "(1) It is pointed out that the method of vaccination by mouth is not new. It was used more than nineteen years ago in an effort to produce immunity to the Shiga type of bacillary dysentery. Renewed interest in the problem followed Besredka's experiments, in which he introduced the use of beef bile as an erosive agent, preparing the way for the entrance of the subsequently ingested bacilli into the deeper lying cells of the mucosa, which he considered responsible for the local immunity. (2) A brief review of some of the early work is given, and also of the work done since Besredka's experiments, including a few of the experiments (foreign) on man. These experiments are somewhat contradictory in that at least a part of the animal experiments do not seem to confirm the work of Besredka, while all of the human experiments favor this method of vaccination. The human experiments are, however, too few in number to warrant definite conclusions. (3) The author's experiments with rabbits show that the greatest protection (70 per cent) was afforded by the subcutaneous method, but that a fair degree of protection (57 per cent) resulted from the vaccination by mouth, and that there was much less danger involved in the use of the latter method. Beef bile is shown not to be necessary in vaccinating by mouth against the Shiga type of bacillary dysentery.

"CONCLUSIONS. While the method of vaccinating by mouth against the Shiga type of bacillary dysentery should still be considered in the experimental stage, two facts are evident: (1) The danger and discomfort are too great to recommend the use of the subcutaneous method of vaccination against the Shiga type of infection. (2) Since vaccines can be so prepared that no danger nor discomfort follows their ingestion, and since at least some immunity is shown to follow such procedure, vaccination by mouth is apparently worthy of further trial."

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 18, 1926

The Thermal Death Point of Protozoan and Metazoan Parasites and the Application of Intra-intestinal Thermal Therapy to the Treatment of Parasitic and Other Affections of the Intestine.—D. DE RIVAS (from the Department of Pathology of the University of Pennsylvania Medical School). Study of the thermal death point of some of the commoner intestinal parasites has led to the development of a method for their eradication from a host by means of heat artificially applied.

The organisms tested and the mode of procedure was as follows: *Endamœba histolytica:* Fresh cover-glass preparations, sealed with vaseline to prevent evaporation, were made of the mucous discharge of a case of amebic dysentery. From 25 to more than 100 actively motile amebæ could be seen in a single high-power field. Cestodes: The head and neck of live tape-worms, *Dipylidium caninum*, *Himenolepis nana* and *Tænia serrata* were mounted in hanging-drop slides in salt solution and sealed with vaseline. Several preparations were made, each containing from three to five scolices. Nematodes: Fresh live specimens of *Ascaris canis*, *Ascaris marginata*, *Uncinaria caninum* and *Trichocephalus trichiura* were placed in dishes containing salt solution. Several parasites, from 3 to 5, were placed in each. The effects of each of the following temperatures was studied upon all the organisms mentioned: 22, 37, 40, 42–3, 45, 47, 50, 55, and 60° C. The following statements apply to all: Temperatures of 50° and higher killed all the organisms subjected to it within three minutes or less. The temperature of 47° C. killed all within five minutes, a few only being active after one or two minutes. At 45° C. few were active after five minutes and all were dead in ten minutes. At 42 to 43° C., a few amebæ were alive after one hour; all dead after two hours; a few cestodes were alive after thirty minutes; all were dead after one hour; a few nematodes were alive after six hours and all dead after eight hours. At 40° C. all the parasites were dead after twelve hours. In applying these results to the problem of eradicating intestinal parasites, dogs were subjected to intraduodenal lavage with salt solution at 45° or at 47° C. for a short time. This was followed by the administration of a hot solution of magnesium sulphate; rapid and complete rectal evacuation of the intestinal parasites of the animal followed without signs of appreciable pathological change of the intestinal mucosa. Similar treatment applied to another animal by means of colonic lavage also produced no appreciable pathological changes in the mucosa of the large intestine. The following method has been employed for the removal of the parasites of the human small intestine (tape-worms, round worms, trichiuris, trematodes, oxyuris, etc.): the duodenal tube is passed through the mouth and, after the flow of bile is freely established, 2 to 3 ounces of a 30 per cent solution of sulphate of magnesium is injected through the tube. This is followed by 500 cc. of hot salt solution at the duodenal temperature of 45° C., a second injection of 2 to 3 ounces of sulphate of magnesium, and then by 500 to 1000 cc, of hot salt solution at the same temperature of 45° C. If necessary a final injection of magnesium sulphate may be used. In from fifteen minutes to one hour from the beginning of the treatment several copious bowel discharges usually occur in which specimens of the parasite are found. For the removal of metazoan parasites of the large intestine and for the treatment of amebic dysentery, colonic lavage with hot salt solution at 45° to 47° C. for five to ten minutes is employed. The temperature is controlled by a thermometer introduced about 4 to 6 inches into the rectum. From 500 to 2000 cc. of salt solution, according to the case and age of the patient, are injected into the colon. The treatment is repeated every other day or every week according to the condition of the patient and the severity, duration and extent of the infection. The symptoms usually subside in a few days or weeks.

The Cause and Prevention of Untoward Effects in the Use of Spinal Anesthesia, as Determined by Experimental and Clinical Investigations.—G. W. WAGONER, J. O. BOWER, J. H. CLARK (from the Department of Surgical Research, University of Pennsylvania School of Medicine). These experiments were made for the purpose of investigating the causes of the production of low blood pressure and shock which have not infrequently been found to follow interspinal injection of local anesthetics. Stovaine, in the form of Babcock's solution or a modification of it, has been used. The modification consisted in the substitution of roseanilin hydrochloride for the lactic acid; its purpose being to identify the distribution of the solution in experiments which were carried out on animals subjected to general anesthesia. In experiments on dogs preliminary laminectomy and exposure of the dura mater was necessary before injection into the subarachnoid space could be made. All the animal experiments were made upon dogs subjected either to general anesthesia by luminal, morphine or ether or to local anesthesia. Arterial blood pressure was recorded by a mercury manometer; respiratory movements either by a pneumograph about the chest or a Jackson pleural cannula and tambour. Cerebrospinal fluid pressure was measured by a water manometer. The average dose of 6 centigrams of stovaine for a 150-pound man was used as the basis for computation of animal dosage. It was repeatedly found that the cerebrospinal fluid pressure is greater at the level of the cisterna magna than at the level of the third lumbar interspace when the patient is sitting. This was confirmed in the dog. It may be concluded that the cerebrospinal system functions as a hydrodynamic rather than as a hydrostatic mechanism. Five controllable factors determine the spread of the injected anesthetic in the subarachnoid space: 1. Existing pressure in the fluid; (2) volume of injected solution ; (3) character of injected solution; (4) force of injection; (5) position of the patient. Observations were made which indicate selective action on sensory roots of the cord and this is believed to be due to an action upon the ganglion cells of the spinal ganglionic chain rather than upon anterior or posterior nerve roots. Fall in general blood pressure is not due to splanchnic dilatation. It does not occur unless the anesthetic extends above the level of the seventh thoracic segment, *i. e.*, the upper limit of the origin of the splanchnic nerves. When it occurs, it is always preceded by respiratory embarrassment—change in type of breathing and decrease in rate and amplitude of respiratory movements. The respiratory effect results from action upon the nerves supplying the intercostal muscles, the phrenic nerves and the respiratory center, and depends upon the height to which the injected drug rises in the subarachnoid space. Graphic records of the respiratory action have been made in man. The usual untoward effects in man may be eliminated by choosing the third lumbar interspace as the site of injection, by reducing the spinal pressure to 10 mm. Hg in the sitting position, by scrupulous intermixture of solution to be injected with spinal fluid withdrawn, by gradual injection of this mixture and by keeping the level of anesthesia below the sixth rib.

The Relation of Antigen and Antibody to Anaphylaxis.—E. L. OPIE and J. FURTH (from the Henry Phipps Institute, University of Penn-

sylvania, Philadelphia). These experiments were undertaken to determine the relation of antigen (horse serum or egg white) to antibody in the production of anaphylaxis. It has seemed not improbable that anaphylactic shock might be produced when antigen and antibody come together, irrespective of the order of their introduction into the body. Young rabbits have been used. Horse serum (0.05 to 2 cc.) has been injected into the peritoneal cavity or into the ear vein and, after an interval of from twelve to twenty hours, anti-horse serum (10 to 20 cc) has been injected into the vein. Characteristic symptoms of anaphylactic shock occur. Anti-horse serum has caused no shock provided the presence of antigen is excluded. When injection of horse serum into one ear vein is followed immediately by injection of anti-horse serum into a vein of the opposite ear, mild shock occurs in most instances, but is less frequent and less severe than in those instances in which an interval of four hours elapses between the injections. In animals in which the interval between the injection of antigen and of antiserum has been four hours, shock has been much less severe than in animals in which the interval has been from twelve to twenty-four hours. It is evident that the intensity of sensitization increases gradually from the time of injection and reaches a maximum intensity after approximately four hours.

The production of desensitization has emphasized the parallel between reversed passive anaphylaxis and the procedure usually employed for the production of passive anaphylaxis. Rabbits sensitized to the action of anti-horse serum by a preliminary injection of horse serum, may be desensitized by repeated injections of anti-horse serum in quantities insufficient to produce symptoms.

When antigen and antibody meet by way of the blood stream, anaphylactic shock occurs, irrespective of the order of their introduction into the body. The period of incubation necessary to produce maximum sensitization indicates that either antigen or antibody must enter into the cells in order to produce sensitization to the other. Anaphylactic shock occurs when antigen and antibody meet within smooth muscle fibers or other cells in concentration sufficient to produce stimulation or injury. It is unnecessary to assume the sudden formation of toxic substance of anaphylatoxin with the power to produce anaphylactic shock.

The Utilization of Carbohydrates.—J. G. Reinhold and W. G. Karr (from the Laboratories of Biochemistry of the Philadelphia General Hospital and the Graduate School of Medicine of the University of Pennsylvania). In a previous communication (V. du Vigneaud and W. G. Karr, *J. Biol. Chem.*, 1925, **66**, 281) an attempt was made to study some of the factors concerned with the rate of disappearance of glucose from the blood after a glucose meal. It was thought that this study might clarify the varied interpretations that are now given to the ordinary sugar tolerance test in clinical diagnosis. It was found in rabbits that fasting invariably decreased the rate of disappearance of blood sugar after the hyperglycemia produced by glucose administration. It was also found that after a four day fast a small protein meal eighteen hours before the tolerance test greatly increased the rate of disappearance, while sugar had only a moderate effect and fat even

decreased the rate of disappearance. If repeated glucose meals are given about two hours apart, the first stimulates the mechanism removing sugar from the blood to such an extent that there is little or no hyperglycemia produced by the second. The present communication has to do principally with the effect of fasting on the utilization of the other simple mono- and disaccharides, and also of starch. When lactose, starch and levulose are given orally in quantities of 3 gm. per kg. of body weight there is very good utilization. The blood sugar seldom rises to over 150 mg. from a normal of about 125 mg. per 100 cc. A period of four days of fasting does not increase the hyperglycemia. If the meal is increased to 6 gm. per kg. then fasting does decrease the rate of disappearance from the blood. Galactose is not as readily utilized as other sugars and a meal of 1.5 gm. per kg. produces a marked hyperglycemia which is is further increased after fasting. Sucrose (3 gm. per kg.) similar to lactose, starch and levulose, is well utilized, but there is an increased hyperglycemia after fasting. Maltose (3 gm. per kg.) is not as well utilized as sucrose, but there is no decrease in the rate of disappearance of the sugar from the blood after fasting. The explanation for these peculiar phenomena is not evident. It is difficult to explain why an equivalent amount of galactose in the form of lactose is so much better utilized than the same amount of pure galactose. Very little lactose was lost in the urine in these experiments. Repeated glucose meals show a stimulation of the mechanism for removing sugar from the blood. On the other hand, a lactose meal, followed in two hours by glucose, gives the same characteristic hyperglycemia as observed when no lactose had been given. The lactose did not stimulate the mechanism which removes glucose from the blood although it was better utilized than the glucose.

Notice to Contributors.—Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, Philadelphia General Hospital, 34th Street, below Pine, Philadelphia, Pa.

Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the article and should be complete, that is, author's name, title of article, journal, year, volume and page (beginning and ending).

Two hundred and fifty reprints are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for this JOURNAL, will be translated at its expense.